ACTA PATHOLOGICA ET MICROBIOLOGICA SCANDINAVICA
SUPPLEMENTUM LX

FROM THE PATHOLOGICAL INSTITUTION AT THE UNIVERSITY
OF UPPSALA. CHIEF: PROFESSOR ROBIN FÅHRÆUS

Jan Mellgren

THE ANTERIOR PITUITARY IN HYPERFUNCTION OF THE ADRENAL CORTEX

An Anatomical Study with Special Reference to Syndroma Morgagni and Notes on Prostatic Hypertrophy

EJNAR MUNKSGAARD · KOPENHAGEN
1945

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UPPSALA 1945

ALMQVIST & WIKSELLS BOKTRYCKERI AB

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INAUGURAL DISSERTATION

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CHAPTER I

INTRODUCTION

The anterior lobe of the hypophysis holds an undisputed front place among the endocrine organs. The literature bearing on the normal and pathological functions of this organ as seen from the viewpoints of the physiologist and the chemist is enormous. On the other hand, relatively little is definitely known about the morphological correlate to the different functions of the organ, particularly in man.

This deficiency can probably be attributed in large measure to inadequately exact methods of pituitary investigation. Thus, as regards man, only normal material has been subjected to quantitative histological investigations on any very large scale, *i. e.* differential count of the cell types of the anterior pituitary gland, though this is usual only in respect of the three well-known main groups: acidophiles, basophiles, and chromophobes. On the other hand, there has not hitherto been any quantitative registration of the special cell types which in ordinary histological investigations seem to characterise certain pathological conditions.

The primary aim of this thesis is to take a registration method of this kind, specially worked out for the purpose, and with its help to determine the morphological characteristics distinguishing the human anterior pituitary when the adrenal cortex is concurrently in a state of enhanced function.

A study of the literature shows that, apart from the few known cases of so-called feminization in men, only two clinical forms of disease are with certainty characterised by enhanced function of the adrenal cortex, namely Cushing's syndrome and virilism (the latter possibly with definite exceptions, however). These two forms of disease have therefore been chosen as starting-points of the investigation.

On the other hand, it has been assumed that certain syndromes found mainly in women during the menopause may, on account of their external likeness to Cushing's disease, be regarded as mild forms of this latter complaint. This is thought to be the case with Syndroma Morgagni, characterised by obesity, hirsutism and frontal enostoses, as also with the similar condition without enostoses. An attempt to confirm this assumption patho-anatomically is an important part of this thesis.

The material for investigation consisted of the endocrine organs from cases of the syndromes mentioned and — for comparison — the same organs from cases of certain other endocrine diseases, and from endocrinely normal subjects. The organs were investigated in respect of weight, macroscopic anatomy, and histology. It was necessary to use the special method for counting cells in the anterior pituitary lobe, to be able to determine the relatively slight changes in these organs in Syndroma Morgagni and similar conditions.

During the course of the work, certain observations have been made concerning the histology of the hypophysis in those cases of prostatic hypertrophy included in the comparison material. These observations were able to indicate that cases of prostatic hypertrophy were characterised by the same pituitary change as Syndroma Morgagni. The question of prostatic hypertrophy's genetic similarity, as regards patho-anatomy, with the other above-mentioned forms of disease has therefore been taken up by the side of the main problem.

Finally, the ultimate aim will be to try to clarify the functional correlation between the anterior pituitary lobe and the adrenal cortex in the forms of disease mentioned, as far as this is possible on the earlier literature in this field, and on the author's own morphological observations.

CHAPTER II

REVIEW OF THE LITERATURE

1. THE ADRENOGENITAL SYNDROME

Addison's noteworthy work of 1855 clarified at one blow the main features of the disease picture arising in lowered function of the adrenal cortex. The homogeneous syndrome dominated by asthenia, anaemia, pigment derangements and lethal issue could be complemented by later research with the symptoms of low blood pressure and disturbances in the electrolyte metabolism, whereas the symptoms of lowered sexual function only play a subordinate rôle in the clinical picture of Addison's disease.

Our knowledge of pathologically increased function of the adrenal cortex, on the other hand, is of later date, and developed along different lines. The oldest of these is based on Bulloch and Sequeira's work of 1905. These authors compiled twelve cases of children with precocious sexual development and hirsutism, which in all cases were combined with either hyperplasia or cancer of the adrenal cortex. In a comparison material of fourteen children with tumours of the adrenal cortex but without disturbances in sexual development, Bulloch and Sequeira only found two epithelial tumours; they therefore concluded that the cortex of the adrenal gland was in some way linked up with the symptoms mentioned.

Works by Apert (1910), Gallais (1912) and others have shown that, in the adult woman, also, certain sexual disturbances in the form of virilism symptoms and, in particular, hirsutism, may appear with epithelial tumours in the adrenal cortex, sometimes associated with obesity.

For a long time, however, the causal connection remained obscure. On the one hand there was no explanation why

certain epithelial tumours of the adrenal cortex might be assumed to induce virilism, etc., and others not. On the other hand, similar syndromes occurred with certain tumours in other endocrine organs, such as the testes, the ovaries, and the epiphysis. It was only with the regressive results of the extirpation of adrenal cortex tumours (Collett 1924; Holmes 1925; and others) and extirpation of hypertrophic or normal-sized adrenals without tumours (Broster *et al.* 1933; and others) that one could definitively show which syndromes were — wholly or in part — induced by increased function of the adrenal cortex.

The literature of the last decades on this subject is comprehensive, and includes several surveys and monographs where clinical aspects in particular are given detailed treatment (Broster, Vines *et al.* 1933 and 1938; Grollman 1936; Bauer 1936 a, b; Berblinger 1936; Kessel 1936; Young 1937; Haymaker *et al.* 1938; Reilly *et al.* 1939; Neumann 1942; Cahill *et al.* 1942).

Clinical Forms

Two kinds of clinical syndromes are nowadays generally recognised as due to pathological hyperfunction of the adrenal cortex. These are on the one hand certain forms of virilism (together with the rare cases of feminization in man), and on the other Cushing's syndrome. One can, with Wintersteiner (1941), include them all in 'the adrenogenital syndrome', defined as 'all conditions in which the abnormal change in the sexual sphere are referable to organic or functional disturbances in the adrenal cortex.' Consequently, cases of the adrenogenital syndrome with virilism symptoms will here be denoted 'adrenal virilism' (a designation originally used by Apert in 1910 to denote a similar syndrome in adult women).

Adrenal virilism

The cases in this group show different clinical symptoms according to the patient's sex, and the age at which the disease set in. Thus, one can follow Broster and co-

workers (1933, 1934, 1938, 1944), whose original scheme is followed in essentials by later authors, in distinguishing between 1) a syndrome of prepubertal virilism in girls and boys, 2) pure virilism in women between puberty and the menopause, and 3) mild virilism in women, together with obesity and other symptoms which the authors collected under the head 'the pluriglandular syndrome'. A final group drawn up by Broster and co-workers covered virilism in women during the menopause. This latter group will be discussed in a special chapter (see p. 31).

All forms of adrenal virilism are characterised primarily by hirsutism of masculine type, often excessive and spreading over large parts of the body. Among the most constant symptoms, furthermore, belong hypertrophy of the clitoris in the female individuals and of the penis in the males. A tendency towards a deep voice, greater muscular development and heavier build, resembling the adult male, is shown by all the clinical groups, though more often and to a greater degree among the younger individuals.

Obesity, usually of 'the buffalo type' (fat localised at the face, neck and trunk, specially the shoulders and abdomen; thin forearms and legs), osteoporosis, glycosuria, striae cutaneae and hypertonia, *i. e.* certain symptoms also included in Cushing's syndrome, are common and often dominant among adult women with adrenal virilism. It is these cases that Broster and co-workers (1933, 1938) relegated to a certain group, the above-mentioned 'pluriglandular syndrome'. These authors had nevertheless to confess that 'the pluriglandular syndrome' can no more be distinctly marked off from 'pure virilism' in women than it can from Cushing's syndrome. This has been confirmed by numerous other authors (Cushing 1932; Hare *et al.* 1935; Bauer 1936 b; Berblinger 1936; Kessel 1936; and others). It should, however, be stated that even the prepubertal cases of virilism may show all the mentioned symptoms of Cushing's syndrome. They are admittedly unusual among girls (Reilly *et al.* 1939), but boys present them often (Cahill *et al.* 1942).

It appears from the above that both the clinical division of adrenal virilism into different groups, and its differentiation

from Cushing's syndrome, are artificial in many respects, and consequently of minor importance for the genetic discussion.

This is probably also the case with certain symptoms which appear in the prepubertal subjects but not in the adult women, namely rapid body growth, accelerated skeletal development, and occlusion of the epiphyses (Bulloch and Sequeira 1905; Broster *et al.* 1933, 1934, 1938; Reilly *et al.* 1939; Cahill *et al.* 1942; Broster 1944; Zondek 1944): Cahill and co-workers maintain (1942) that these symptoms are not necessarily due to anything else than the factors inducing the virilism symptoms common to all the groups (see below).

As regards the internal genital organs in adrenal virilism, the adult females usually show atrophy of the ovaries with absence of follicles or corpora lutea, or else follicular cystic degeneration and atrophy of the other internal genital organs, and amenorrhoea (Broster *et al.* 1934, 1938, 1944; Westman 1941). Girls with adrenal virilism show the same state of affairs, in that the internal genital organs are normal or hypoplastic and the menses seldom commence even when the patient has reached puberty (Bulloch *et al.* 1905, Reilly *et al.* 1939). It should, however, be mentioned that, in single cases, traits of true feminine precocity (menses, development of the breasts) may come into the picture (Broster *et al.* 1933; Reilly *et al.* 1939; Westman 1941). On the other hand, the boys with virilism present varying development of the testes, prostate and seminal vesicles; hypertrophy of the testes, prostatic secretion and sperm have been observed (Cahill *et al.* 1942).

ADRENAL FEMINIZATION

That males are also liable to heterosexual adrenal effect is shown by the eight known cases of cancer of the adrenal cortex in adult men with so-called feminization, *i. e.* atrophy of testes (established in four or five cases) and growth of the breasts — in two cases even secreting breasts (cf. surveys by Roholm and Teilum 1942; Kooyman 1940). In this group, too, extirpation of the adrenal tumour with subsequent return to

health has proved the genetic significance of the tumour (Holl 1930).

CUSHING'S SYNDROME

The nowadays familiar clinical picture which has been described by Cushing 1932 was soon acknowledged as a uniform syndrome. Cushing himself considered the disease picture in question to be induced by a basophile adenoma in the anterior pituitary, since an adenoma of this kind was presented by 12 of the 14 cases with the syndrome which he compiled in 1932. However, most of the cases also showed hypertrophy of the adrenal cortex. Cushing therefore maintained that the pathogenesis of the syndrome might also include a hyperfunction of the adrenal cortex, possibly secondary to the hypophyseal change. This idea had already been advanced by Bauer, who in 1930 published a case of 'Ueberfunction des Nebennierensystems' (*i. e.* Cushing's syndrome), with basophile adenoma in the anterior pituitary. It is true that the dominating importance of the basophile adenoma could not be upheld; nevertheless, later observations have confirmed the conception that a raised function of both the anterior pituitary and the adrenal cortex play a part in the genesis of this disease picture (see below).

As is known, Cushing's syndrome occurs mainly in adult women before the menopause, and is characterised by obesity of 'the buffalo type', with 'moon face', hirsutism of the face, and purplish striae cutaneae on the lower abdomen and the thighs. Osteoporosis, polycytaemia, hypertonia, glycosuria and high blood cholesterol readings are the rule. The basal metabolism is as a rule low, sometimes raised; the blood calcium is in some cases raised, with negative calcium balance (Cushing 1932; Jores 1939; Malaguzzi-Valeri 1940; Cahill *et al.* 1942; Zondek 1944). Unlike adrenal virilism, Cushing's syndrome in women often does not include male pubic hair and hypertrophy of the clitoris. The frequent occurrence of transitional types to pronounced virilism has often been pointed out, however (cf. above). Furthermore, it is usual for women with Cushing's syndrome as well as those with adrenal virilism to show amenorrhoea; the ovarian changes are either the same as in

virilism or else cystic degeneration with luteinization (Cushing 1932; Bergstrand 1934; Berblinger 1936, 1943). When Cushing's syndrome has appeared in men, atrophy of the testes and lowered sexual functions have been found (Cushing 1932; and others), as also in adrenal feminization. However, the lowered sexual function and atrophy of the gonads are no more constant in Cushing's syndrome than they are in adrenal virilism and feminization (Broster *et al.* 1933; Reilly *et al.* 1939; Holl 1930; Berblinger 1936, 1940; Malaguzzi-Valeri 1940).

The results of adrenal operations have been bad in cases of Cushing's syndrome; the patient has often died from adrenal insufficiency following the extirpation of a cortex tumour, since in these cases the second adrenal was often atrophic (Cahill *et al.* 1942). However, by extirpating a cortex tumour in 1942, Cahill showed that such a growth may, in a complete Cushing's syndrome, be responsible for at least loss of libido, amenorrhoea and hirsutism. Other authors have derived improvement from extirpation of an adrenal with hyperplastic cortex (Broster *et al.* 1933, 1938; Crile 1934; Luft 1944) or denervation of the adrenals in Cushing's syndrome (Crile 1934; McCullagh and Cuyler 1937).

Summing up, then, we can say that certain important symptoms of Cushing's syndrome (above all sexual disturbances and hirsutism) may, like all forms of adrenal virilism, be attributed to a hyperfunction of the adrenal cortex.

SPECIAL FORMS. DELIMITATION

Some further syndromes must be surveyed, since they have points of contact with the adrenogenital syndromes.

Thus, it has been thought that hermaphroditism (Pseudohermaphroditismus femininus, pseudohermaphroditismus masculinus and hermaphroditismus ambiglandularis) might appear as a form of virilization in female foetuses, resulting from adrenocortical hyperfunction during early growth (Marchand 1891; Gallais 1912; Broster *et al.* 1933, 1938; and others). However, there are still insufficient endocrine and embryological data to determine whether a given case of human herm-

aphroditism presents zygotic or hormonal intersex (Goldschmidt 1931; Moszkowitz 1936; Lindvall and Wahlgren 1940). This group will therefore not be included in this thesis.

All syndromes of sexual derangement in tumours of the testes, ovaries, and epiphysis must similarly be omitted. Some of them admittedly bear great clinical resemblances to the adrenal disease pictures; with the exception of some isolated cases (personal communication from Rasmussen; cf. Dunn 1938), however, the former have not been investigated for disturbances of the adrenal cortex or hypophysis. It is therefore not yet clear whether there is a connection between the former syndromes and the adrenogenital group.

Anatomical Findings

the adrenal cortex

Macroscopical. In this respect, the adrenal cortex has varied as much in the different virilism syndromes as in Cushing's syndrome. Thus, cortical cancer and adenoma have often been found in all groups (Bevan and Romkild 1802; Linser 1903; Bulloch *et al.* 1905; Holmes 1925; Cushing 1932; Broster, Vines *et al.* 1933, 1938; Hare *et al.* 1935; Bauer 1936 a, b; Berblinger 1936; Reilly *et al.* 1939; Malaguzzi-Valeri 1940; Cahill *et al.* 1942). Simple hyperplasia of the adrenal cortex without tumour has been found to be common in all ages among females with virilism, as in Cushing's syndrome (Cushing 1932; Broster *et al.* 1933, 1934, 1938; Reilly *et al.* 1939; Malaguzzi-Valeri 1940; Cahill *et al.* 1942). Simple hyperplasia has been stated not to occur among boys with adrenal virilism (Jores 1939); it is admittedly uncommon, but macrogenitosomia praecox in simple hyperplasia of the adrenal cortex nevertheless does occur (Cahill *et al.* 1942; Mellgren 1942). Hyperplasia of aberrant adrenal cortex tissue has been observed in some cases of adrenal virilism in girls (Marchand 1891, Reilly *et al.* 1939).

As in Cushing's syndrome, symptoms of virilism in adult women have in a number of cases been observed without

hypertrophy or tumour of the adrenal cortex, and without tumour being demonstrated in any other endocrine organ. Operation results have shown that such cases could belong to the adrenal type (Broster *et al.* 1933, 1938). It is not certain that women form an exception in this respect, however, since the older literature in particular has reported numerous cases of virilism in boys, no change in the adrenals or other endocrine organs being demonstrable (Leiner 1920; Cahill *et al.* 1942). The negative data are in some cases obviously due to inadequate investigation, but it is also conceivable that the cases mentioned also contain such as are of adrenal type but without grossly hypertrophic adrenal cortex.

On the other hand, it is well known that epithelial tumours in the adrenal cortex occur more often without endocrine disturbances than with them (Goldziher 1929; Geschickter 1935; Broster *et al.* 1938; McGavack 1940; Sudds 1940).

Microscopical. Ponceau-Fuchsin Reaction. If, then, the gross adrenal changes in the adrenogenital syndrome are inconstant, the microscopic changes are no less so. Grollman's theory (1936) that the so-called x-zone observed by him is associated with the adrenogenital syndrome has not been substantiated (Cramer *et al.* 1937; Broster *et al.* 1938; Verzár 1939; Cahill *et al.* 1942; and others). It has subsequently been abandoned by Grollman himself (Gersh and Grollman 1939). Cahill and co-workers (1942) have found the amount of vacuoles present in the adrenal cortical cancers to be more marked, the nearer the syndrome approached the Cushing type.

Far greater importance seems to attach to Vines's so-called Ponceau-Fuchsin Reaction (PFR). Using a special staining method on operation material, Vines found (Broster, Vines *et al.* 1933, 1938) an abundance of fuchsinophile granules in the macroscopically normal or hypertrophic adrenal cortex in 34 of 36 women with adrenal virilism, while the reaction was negative in the cortex of 6 cases without endocrine disturbances. Further, the PFR was found to be positive in the tumours in 5 cases with cortical cancer and virilism, but

negative in 5 cases of this cancer without virilism. In 6 Cushing cases the results varied; in 3 men it was negative; in 2 women it was negative, and in 4 positive. Moreover, Vines saw a positive reaction in the adrenal cortex of endocrinely normal autopsy cases in 26 % of the men over 40 years of age, and in 48 % of the women over 40 years of age. However, the reaction in this control material was never so strongly positive as in the cases with virilism, appearing only as isolated granulated cells or small scattered groups of such cells. From these findings, and from certain biochemical observations (see below), Vines drew the conclusion that the fuchsinophile substance was in some way bound up with the virilising action of the adrenal cortex, and was possibly identical with a virilising adrenal cortex hormone or its pre-hormone.

Certain authors have been able to confirm Vines's observations. Thus, Lescher and co-workers (1935) found a positive reaction in a case of virilising adrenal cortex cancer in a woman. Cahill and co-workers (1942) observed positive PFR in all adrenal cortex tumours, though it was stronger in cases with the adrenogenital syndrome. The present author, too, found the PFR positive — though only in the form of small fuchsinophile cell groups — in two adrenal cortex tumours with adrenal virilism in women, and a strongly positive reaction in the hypertrophic adrenal cortex of a case of precocious puberty in a boy (1942). In a case resembling the last-mentioned one, Luft (1944), too, found positive PFR. Anderson and co-workers (1943) have also found a positive reaction, though not very pronounced, in a virilising adrenal cortex cancer in a young woman. Further, Webb (1934) and Hare and co-workers (1935) found positive PFR in adrenal cortex cancer in Cushing's disease, and in the same disease Luft (1944) found the reaction to be weakly positive in two cases, but negative in four. The PFR was weakly positive in one of two adrenal cortex adenomas from women with faint virilism and Cushing symptoms observed by Westman (1941). On the other hand, McGavack (1940) was able to establish negative PFR in an adrenal cortex cancer with virilism, but he himself states that this may be assignable to certain cited technical

difficulties in this special case. Luft (1944) found negative PFR in the adrenal cortex of several cases with hirsutism in women, who did not, however, present any other symptoms of virilism. Finally, Simpson and Joll (1938) and Roholm and Teilum (1942) were able to establish a negative reaction in feminizing adrenal cortex cancer in men.

Apart from the above-mentioned works by Vines and by Cahill and co-workers, there does not seem to have been any systematic investigation into the PFR in pronounced virilism. On the other hand, Sudds (1940) has investigated the reaction in a large control material. She found fuchsinophile granules in 24 % of adult male adrenals, and in 28 % of female adrenals. The reaction was regularly negative under the age of 24 years, and its frequency increased with age, specially in the women. Apart from a few cases with strongly positive PFR (she does not say how many), Sudds's results do not seem to conflict with those of Vines as regards weakly positive reaction in certain older individuals. It is therefore very likely that strongly positive PFR is positively correlated with adrenal virilism, independent of the size of the adrenal cortex. The weakly positive reaction which Vines and Sudds observed in older men and women will be discussed in connection with the menopausal syndromes and prostatic hypertrophy (see below).

The remarkable discovery of PFR can call into question the accuracy of the whole idea that there is a *hyper*-function of the adrenal cortex. As the fuchsinophile granules preponderate in virilism but not in feminization, and occur irregularly in Cushing's syndrome, the PFR might rather indicate a pure *dys*-function, *i. e.* production of a pathological hormone. A circumstance arguing against this, however, is that the fuchsinophile granules also appear, though as a rule in smaller numbers, in the adrenal cortex in cases without outstanding endocrine characteristics. Nevertheless, the PFR has obviously made it likely that a certain normal partial function of the adrenal cortex may be enhanced in pathological virilism.

OTHER ENDOCRINE ORGANS

No other organs than the adrenals, gonads and hypophysis have received such systematic investigation in connection with the adrenogenital syndrome. In some cases of Cushing's syndrome the parathyroid glands have been enlarged (van Buchem 1941), but were usually found to be normal, at least macroscopically, even in the presence of osteoporosis (Bergstrand 1934; Gellerstedt *et al.* 1939; van Buchem 1941; Luft 1944). The thymus has in some cases been found to be atrophic in the adrenogenital syndrome (Cushing 1932; Bergstrand 1934), but to be normal in a number of others (Luft 1944). It is noteworthy that thymoma or thymus cancer has been observed in a few cases of typical Cushing's syndrome (Crooke 1935). In many cases of Cushing's syndrome the thyroid has been normal; it has often been small, with histological signs of hypofunction, and in a few cases showed histological signs of enhanced function (Cushing 1932; Bergstrand 1934; Gellerstedt *et al.* 1939; Cahill *et al.* 1942; Luft 1944). In adrenal virilism and feminization the thyroid may be anatomically and histologically normal (Broster *et al.* 1938; Westman 1941; Roholm *et al.* 1942; and others). Normal histology has often been reported for the pancreatic islets (Cushing 1932; Bergstrand 1934; Gellerstedt *et al.* 1939; Westman 1941); however, there seem to be no investigations with special technique, such as that of Ferner (1942). Finally, the epiphysis has been found normal in various forms of the adrenogenital syndrome (Gellerstedt *et al.* 1939; Westman 1941; Cahill *et al.* 1942; Roholm *et al.* 1942; Luft 1944).

THE ANTERIOR PITUITARY

It could soon be shown that basophile adenomas (or mixed basophile-chromophobe adenomas) in the anterior pituitary were far less common in Cushing's syndrome than Cushing assumed. According to Tesseraux (1937), Raab (*cit.* Jacobi *et al.* 1939), Malaguzzi-Valeri (1940) and others, basophile adenoma in the anterior pituitary could be demonstrated in only about half of all cases with Cushing's syndrome. It is true that, in

a number of these cases, adenomas of this kind might have escaped detection, since they are usually small, but numerous Cushing cases with hypophyses cut in series and without adenoma have also been reported (Crooke 1935; Gellerstedt *et al.* 1938 a, 1939; and others). On the other hand, basophile pituitary adenomas not infrequently occur without perceptible endocrine disturbances, though obviously less often than in Cushing's syndrome (Costello 1935; Susman 1935; Ecker 1938). Some Cushing cases without basophile pituitary adenoma have instead been reported to show a diffuse hyperplasia of the basophile cells in the anterior pituitary (cf. survey by Malaguzzi-Valeri 1940). These reports must be taken cautiously, however, since no differential count has been made (cf. Rasmussen 1929). Finally, chromophobe, acidophile, or indeterminable adenomas have also been found at times in a number of hypophyses in connection with Cushing's syndrome (cf. Gellerstedt *et al.* 1938 a, 1939; Malaguzzi-Valeri 1940).

The Hyaline Change. In this situation, a discovery by Crooke is of the greatest importance. In 1935, this author observed the anterior pituitary of 12 cases with typical Cushing's syndrome to show a characteristic change in the basophile cells, which he called the hyaline change. The pathological cells were typified by structureless granule-free fields in the cytoplasm and remains of basophile granules. As a rule they had a large cellular body and one or more large nuclei, poor in chromatin and sometimes polymorphous, together with well-preserved Golgi apparatus (Hare, Ross and Crooke 1935; Crooke 1935). Six of Crooke's cases also had a basophile adenoma. The hyaline change did not occur in the adenoma, however, but in the remaining part of the anterior pituitary outside it. In the control material consisting of anterior pituitaries from persons without signs of Cushing's syndrome, Crooke found only a few basophiles with hyaline change in 9 hypophyses of 350.

Crooke's observation of hyaline change in Cushing's syndrome has been verified by many investigators (Fuller and Russell 1936; Rasmussen *et. al.* 1936, 1938; Gellerstedt 1938 a, 1939; Ulrich

1939; van Buchem 1941; Cahill *et al.* 1942; Luft 1944; and others). Like Crooke, they usually found the hyaline change in the anterior pituitary *outside* a basophile adenoma (or in the absence of an adenoma); only rarely have hyaline basophiles occured *in* an adenoma of this kind (Gellerstedt 1938 a, 1939; Ecker 1938). Graef and co-workers further observed (1936) the same change in Cushing's syndrome, independent of Crooke, but laid special stress on the state of the nuclei (vesicular change). Like Graef *et al.* (1936) — and subsequently the present author (1942) — Gellerstedt also maintained (1939) that, as well as the hyaline basophiles, the anterior pituitary in Cushing's syndrome sometimes contained numerous large granule-free cells with foamy protoplasm and large nuclei, poor in chromatin and at times polymorphous. These hypertrophic amphophiles, which Gellerstedt compares with the normally occurring 'entgranulierte Chromophilen' of Kraus (1926), have been taken to be a later stage of the degranulation of the basophile in the hyaline change, since numerous transitional types between the hyaline basophiles and the hypertrophic amphophiles could be observed.

On the other hand, Crooke's observations have sometimes been sceptically received. Several authors have entirely disregarded the hyaline change, or not been able to find it in Cushing's syndrome (Bauer 1936 a, b; Cohen and Dibble 1936; Erdheim, who investigated the Urban case, 1937; Jacobi and Tigges 1939; McGavack 1940; Schultze, who investigated the Ottmer case, 1942; Baráth 1943; Berblinger 1942, 1943). Kraus (1937 a) wanted to identify the hyaline change with colloid degeneration, which is obviously wrong (Gellerstedt 1939). On the other hand, none of the authors who proved familiar with Crooke's change found it missing in any typical Cushing case (cf. however, Rasmussen *et al.* 1938, on atypical cases). Cushing (in a letter to Ecker 1938) also accepted the hyaline change as 'a common anatomic denominator in all cases with basophilism'.

An apparently weightier objection has been advanced by Ecker (1938), who found among 121 'endocrinely normal' hypophyses 8 with 'a marked degree of the hyaline change', though without nuclear change. Ecker also found hyaline basophiles

of this kind in 4 of 72 basophile adenomas. However, even regardless both of the fact that the cases with hyaline change in the anterior pituitary contained such as had endocrine disturbances (a few cases with obesity and hypertonia, among others), and the fact that Ecker gives no details as to the number of changed basophile cells, her observations hardly disagree with those of Crooke; all they show is that the hyaline change is not absolutely specific to Cushing's syndrome, but is only extremely closely correlated with it.

The hypophysis seems to have been less frequently investigated in connection with *adrenal virilism*. In some cases it has been reported normal, in others it has shown different and apparently unspecific changes, such as cysts, chromophobe adenoma, increased number of acidophiles, increased number of basophiles, absence of basophiles, increased number of chromophobes (Mathias 1922; Moltschanoff *et al.* 1930; Broster *et al.* 1933, 1938; Neumann 1934—35; Westman 1941; Berblinger 1942).

In each of 4 cases of adrenal virilism (3 women and 1 boy), the present author (1942) observed the same changes in the anterior pituitary. While the frequency of normal basophiles varied, all 4 anterior pituitary lobes contained numerous hyaline basophiles, hypertrophic amphophiles with large vesicula-like nuclei, and transitional types between the two. A 5th case, that of an 7-year-old boy with precocious sexual development and pronounced Cushing's syndrome, showed the same change in the anterior pituitary, but here the picture was completely dominated by Crooke's cells (later also published by Luft, 1944). Thus, the special elements were the same as in Cushing's syndrome, although Crooke's cells dominated only in 2 of the virilism cases.

CONCLUSIONS FROM THE ANATOMICAL FINDINGS

As regards the functional importance of the pituitary change in Cushing's syndrome, *i. e.* abundant occurrence of Crooke's cells and the hypertrophic amphophiles derived from them, it has been assumed, partly on purely morphological grounds, that the basophile cells have a hyperfunction: this is suggested

by the size of the cells, the enlarged nuclei whose chromatin is sparse and usually lies peripherally, the large nucleoles, and the state of the Golgi apparatus (Crooke 1935; Gellerstedt 1938 a, 1939; Mellgren 1942; cf. also Caspersson and Santesson 1943). For the same reasons the change can probably not be regressive-degenerative (as Graef *et al.*, 1936, assumed it was). Naturally, the same viewpoints hold for the similar changes in the anterior pituitary of cases with adrenal virilism (Mellgren 1942).

Criticism has, however, been levelled at the conception that cells with a small granule content, such as the hyaline basophiles and the hypertrophic amphophiles, might mean an increased secretory function (Ulrich 1939; Berblinger 1942, 1943; and others). The criticism is based on the familiar fact that, in exocrine organs, granules usually occur abundantly when the secretion is active, and less abundantly when it is not functioning. As regards the basophile granules in the anterior pituitary, P. E. Smith (1923) has shown by experiment that those parts of cattle hypophyses which are richest in basophile granules also have the strongest gonadotropic effect on implantation. Berblinger (1943), furthermore, implanted in mice not only parts of a basophile adenoma but also parts of the remains of the anterior pituitary from a case with Cushing's syndrome. As the adenoma (with profusely granulated cells) gave a corticotropic effect, *i. e.* growth of the adrenal cortex in the experiment animals, but the anterior pituitary remains did not, Berblinger concluded that the adenoma was responsible for the increased secretion of corticotropic pituitary hormone to the blood, which he had found an essential of Cushing's disease. Berblinger's experiment is fundamental, since it seems to provide the first clear proof that the basophile granules are the bearers of the corticotropic hormone. On the other hand, the experiment does not prove that the profusion of basophile granules implies increased *secretion* of corticotropic (or other) hormone, or *vice versa*.

Numerous experiments have furthermore shown that increased hormonal secretion may be concurrent with low concentration of the same hormone in the organ producing it

(for the thyroid cf. Okkels, Krogh *et al.* 1932; for the adrenal cortex and virilising adrenal tumours cf. Broster *et al.* 1938, and Wintersteiner 1941). As regards the anterior pituitary, Severinghaus (1932, 1937, 1939), for one, has shown on the strength of experiments that a degranulation of the basophile cells in rodents can accompany increased gonadotropic and corticotropic function (cf. also Schooley *et al.* 1938). Support is hereby afforded to Gellerstedt's theory that the hyaline basophiles point to a pathologically raised function in which the basophile granules are used up (faster than they are formed is understood). Ecker having shown the normal occurrence of the hyaline change (cf. above), it is less clear histologically whether the supposed raised function is pathological in the sense that an abnormally constituted incretion is produced (Gellerstedt 1939; Mellgren 1942). This question will be discussed in more detail in connection with the syndromes in aging persons.

Even if the hyaline change is the most important pituitary alteration in Cushing's syndrome from a genetic point of view, the presence of a basophile adenoma in the anterior pituitary is positively correlated with the syndrome. Gellerstedt (1938 a, 1939) therefore assumed that the basophile adenomas were the expression of a compensatory regeneration of basophiles on account of the swift consumption of granules. He also showed that the same line of thought may hold for all adenomatous neoformations in the endocrine organs, just as it was previously proved to hold for the thyroid and parathyroid (Bergstrand 1921, 1931, 1938). Obviously, then, malignant basophile adenomas of the anterior pituitary in Cushing's syndrome might also be regarded as reactive neoformations, the fact being that in Bergstrand's case of 1934 — a 42-year-old woman with Cushing's syndrome, hypertrophic adrenals, and a basophile anterior pituitary tumour growing infiltratively — Gellerstedt (1939) found the hyaline change in the anterior pituitary remains. The same viewpoints may obviously also be applied to the tumours of the adrenal cortex. In other words, it is not out of the question that the latter tumours, no matter whether they be benignant or malignant, may be reactive, *i. e.*

are not the prime cause of the disease when they are combined with endocrine symptoms. A further argument for this conception is that the endocrinely active adrenal cortex tumours may be bilateral, or occur together with general cortical hyperplasia (cf. surveys in Broster *et al.* 1938; Roholm *et al.* 1942; Reilly *et al.* 1939; Cahill *et al.* 1942; Luft 1944). Certain discoveries from experiments on animals also point very strongly in the same direction (see below).

SUMMARY

In the adrenogenital syndrome, only the anterior pituitary and the adrenal cortex show changes with any regularity at all. The adrenal cortex varies in all groups from macroscopically normal to great cancer; as a rule it is the site of simple hyperplasia or adenoma. A strongly positive PFR is often found in virilism, independent of the macroscopic appearance. In Cushing's syndrome the anterior pituitary often, and possibly regularly, presents Crooke's hyaline change in the basophile cells, less regularly presenting a basophile adenoma. Pituitary changes resembling those in Cushing's syndrome have been observed in some cases of adrenal virilism. Certain observations suggest that both the pituitary tumours and the adrenal tumours may be reactive — possibly compensatory, and consequently not the prime cause of the disease. Both the anatomical and the clinical evidence obviously points to a connection between pituitary and adrenal changes in Cushing's syndrome. If similar pituitary changes prove to be regular in adrenal virilism, the same pituitary and adrenal correlation should be indicated here as in Cushing's syndrome.

Biochemical and Experimental Observations. Genesis of the Adrenocortical Function

The biochemical view of the adrenogenital syndrome is built up on the discoveries that not only the essential life-preserving substances of corticosterone and desoxycorticosterone can be isolated in pure form from the normal adrenal cortex, but also sex hormones such as adrenosterone (Reichstein 1936),

progesterone (Beall and Reichstein 1938) and oestrone (Beall 1939; and others). Different sex hormones have furthermore been produced from desoxycorticosterone (cf. the survey by Verzár 1941 b). This substantiates the first condition for Vines's conception (1938) that the adrenal cortex can function in the adrenogenital syndrome as a bisexual internal secretion sex gland.

Experiments. Numerous experiments have shown that the adrenal cortex not only contains but can also secrete substances with sexual hormone effect: it cannot be doubted that desoxycorticosterone is normally secreted by the adrenal cortex. It is true that Greene and Burrill (1940), as also Paschkis (1941), reported negative results, but Hooker and Collins (1940) obtained an androgenous effect on cock's combs from desoxycorticosterone, and a similar, but weak effect on the adnexa of rats and mice, while Gros *et al.* (1942) showed androgenous effect from desoxycorticosterone acetate on the adnexa of castrated cats. Moreover, Burrill and Greene (1940) found that the ventral prostate did not atrophy completely in young castrated rats before they had been deprived of their adrenals, and Hodler (1936, 1937) and Moon and co-workers (Davidson and Moon 1936; Davidson 1937) were able, with corticotropic anterior pituitary hormone, to induce hyperplasia of the adrenal cortex and an androgenous adrenal effect on the accessory sex organs of gonadectomized guineapigs and rats. Oestrogenous adrenal cortex effect from desoxycorticosterone was shown on gonadectomized cats by Gros *et al.* (1942), and Moon (1937, b) induced signs of oestrus in immature spayed rats by administration of an adrenotropic extract. A progesterone effect from desoxycorticosterone has been convincingly shown by several authors in experiments on animals (Miescher *et al.* 1938; Fremery *et al.* 1939; Leathem *et al.* 1940; Gros *et al.* 1942; and others), and by Neumann (1942) on gonadectomized women. It has furthermore been made probable that desoxycorticosterone can in rabbits and man be transformed into progesterone (Cuyler *et al.* 1940; Westphal 1942). Finally, it is also known that progesterone has a certain androgenous

effect (Steinach and Kuhn 1931; Lamar 1937; Greene and Burrill 1939; Gros *et al.* 1941). A direct action of adrenal substances on the mammary gland, rendering lactation possible in animals without adrenals, has, finally, been proved by Brownell *et al.* (1933). A theoretical explanation is hereby provided for all the effects on the accessory sex organs and secondary sex characters observed in the adrenogenital syndrome.

However, experiments have also shown a direct connection between the adrenal cortex and the gonads. A suspended cycle is the rule in rats after extirpation of the adrenals (Wyman 1928; Martin 1932; Corey and Britton 1933; Ehrenstein and Britton 1936; Fitzbugh 1937). Here, atrophy of both the female and the male sex organs has also been observed (Fitzbugh 1937). A certain stimulating effect from adrenal extract on both testes and ovaries was found by McKinley and Fischer (1926), as also by Fitzbugh (1937); a similar effect on the ovaries was seen by Ehrenstein *et al.* (1936), while Pottenger *et al.* (1938) found adrenal substance to give atrophy of the ovaries, but growth of the testes and a stronger spermiogenesis. Hoffmann (1937—38) claims to have isolated a water-soluble gonadotropic substance from the adrenal cortex, which substance induces corpora lutea in the ovaries of infant rats.

In view of the conditions of the experiments, however, it is possible that all these gonadotropic effects of adrenal cortex substances were induced via the hypophysis. On the other hand, a gonadotropic effect with the formation of corpora lutea in the ovaries of rats and mice (even when hypophysectomized) has been obtained by Selye and co-workers (1940) with both desoxycorticosterone, progesterone, testosterone and oestradiol in suitable doses. As a rule, however, all these substances produced inhibition of development, stroma atrophy and cystic degeneration of the ovaries.

Apart from Hoffmann's reports, which probably need confirmation (Verzár 1941, b), all the contradictory data as to stimulating or atrophying effect of the adrenal cortex on testes and ovaries can be most simply explained as an effect from the secretion of steroid hormones by the adrenal cortex, the

quantity of the secretion rather than the nature of the steroids being then of importance. The observations of Rubinstein and Kurland (1940), with those of Selye (1941), also suggest this to be the case, these investigators finding that testosterone atrophied or stimulated the testes of rats according to the size of the dose.

However, more symptoms than such as can be directly referred to the sexual sphere have been experimentally induced with sexual hormones or adrenal substances. Moon (1936, 1937 a, b; 1940) has shown that atrophy of the thymus can be induced in rats with corticotropic hormone. Excess of androgens can also produce rapid growth followed by closure of the epiphyses (Rapfogel 1940; McCullagh and McGurl 1940). Increased body weight in man, due to fat apposition, was obtained by several investigators with cortical hormone (cf. Zondek 1944). Reiss (1937) saw hyperplasia of the adrenal cortex and obesity to follow partial hypophysectomy in rats. He believed these effects to be caused by excessive production of corticotropic hormone. On the other hand, it must be admitted that Reiss's experiment is difficult to interpret. Not only the pituitary remains but also the tuber cinereum may have been injured, and such injuries may cause obesity, as Smith showed already in 1923 (cf. van Dyke 1936, Bomskov 1939). Horneck (*cit.* Jores 1939), finally, has induced cutaneous striae with adrenal extract.

Hormone assays. In the biochemical investigation of human subjects with the adrenogenital syndrome, interest has mainly centred round the urine excretion of the sex hormones. That is to say, attempts to determine the electrolytes of the blood or excretion of the life-preserving cortical substances in the urine in this syndrome are still few, and have not as yet yielded uniform results (Anderson and Haymaker 1938; Westman 1941; cf. Luft 1944).

It may be considered established that the adrenal cortex in man is the source of a number of the androgenous and oestrogenous substances normally excreted with the urine (cf. surveys by Wintersteiner 1941, Luft 1944). As a rule, the urine ex-

cretion of androgens has been raised in adrenal virilism (cf. Wintersteiner 1941; Broster *et al.* 1933, 1938; Cahill *et al.* 1936, 1938, 1942; Luft 1944). According to Butler and Marrian (1937, 1938) the excretion of steroids with androgenous effect may also be qualitatively abnormal here. In Cushing's syndrome the data as to androgen excretion are more contradictory. It seems as though cases with adrenal cancer excrete a larger amount of androgens more regularly than those without tumours (Hare *et al.* 1935; Lawrence 1937—38; Crooke *et al.* 1939; McCullagh and Lilga 1940; Drips *et al.* 1940; Luft 1944). However, in 10 cases of Cushing's syndrome without cancer, Luft (1944) found on the average a greater urinary excretion of androgens than in normal women determined photometrically, but no difference between the groups in tests on cock's combs. The data as to urine excretion of oestrogens in virilism and Cushing's syndrome also vary from normal values to 13,000 I.U., probably due in part to differences in technique (cf. surveys by Wintersteiner 1941 and Luft 1944). Using a uniform technique, Luft (1944) found low oestrogen values both in 15 cases of hirsutism in women, and in 10 patients with Cushing's syndrome. The excretion of pregnandiol has, in the few cases of the adrenogenital syndrome where it has been determined, usually been found to be raised (cf. Anderson *et al.* 1943; Luft 1944).

Even if there are certain discrepancies between the amount of excreted androgens on the one hand, and the degree of the virilism symptoms and the PFR on the other (Westman 1941; Anderson *et al.* 1943; Luft 1944), the cited hormone assays unquestionably bear out a quantitatively enhanced adrenocortical function common to the clinical groups which are here treated as forms of the adrenogenital syndrome according to Wintersteiner's definition. When added to clinical, anatomical and experimental data, the hormone assays furthermore show that thymus atrophy, developmental disturbances in children with virilism, obesity, and cutaneous striae may, as well as the disturbances in the gonads and the secondary sex characters, be direct expressions of the cortical hyperfunction.

THE FUNCTIONAL CONNECTION BETWEEN THE ANTERIOR PITUITARY AND THE ADRENAL CORTEX IN THE ADRENOGENITAL SYNDROME

HORMONE ASSAYS CONCERNING THE FUNCTION OF THE ANTERIOR PITUITARY LOBE. The clinical and anatomical findings pointed to an enhanced anterior pituitary function in Cushing's syndrome, and possibly in adrenal virilism also. Using hormone assays, attempts have long been made to verify this conception by investigations into the urine excretion of gonadotropic substances, the only test of raised anterior pituitary secretion in common use. The results have varied, but as a rule the excretion of gonadotropin does not seem to have been raised either in adrenal virilism or in Cushing's syndrome (cf. Luft 1944). On the contrary, Luft found lowered gonadotropin values in Cushing's syndrome and in women with hirsutism.

Naturally, these negative urine findings do not prove that the pituitary function in the adrenogenital syndrome is not raised at all — raised, that is to see, with reference to other substances than the gonadotropic ones. The positive proof of this has also been submitted. In 1935 Jores and Beck worked out a biological test method to determine the amount of corticotropic substance in the blood. The method is based on the weight of the adrenals in normal mice. Even though it can be criticised on the score both that non-hypophysectomized animals were used as test objects (cf. P. E. Smith 1927; Collip *et al.* 1933; and the survey by Anselmino and Hoffmann 1941) and that there seem as yet to be no investigations on a fully trustworthy control material, the method has nevertheless yielded a number of significant results. Thus, using it, Jores (1936) found an increased amount of corticotropic substance in the blood of each of 6 cases with Cushing's syndrome. In 3 cases of Cushing's syndrome published by Jacobi and Tigges (1939) and Sundermann (1940—41), Jores also found raised values for corticotropic substance in the blood. Similar positive results have also been communicated by Brauer (1937) and Berblinger (2 cases; 1940, 1943). Hitherto the method seems to have been tested on only 1 case with pronounced

adrenal virilism (a 20-year-old woman with strong clitoric hypertrophy, among other symptoms; Sundermann 1940—41); in this case, too, there was an increased amount of corticotropic hormone in the blood.

Thus, a high degree of support is lent to the theory that an increased corticotropic pituitary function is an essential feature of Cushing's syndrome, and probably of adrenal virilism also. The hyperfunction of the adrenals and the cortical changes (hyperplasia, adenoma, cancer) may very well be attributed to the increased corticotropic pituitary function.

Experimental data bear out this view. Using castrated female guineapigs, Hodler (1936, 1937) has shown beyond a doubt that the hyperplasia of the adrenal cortex induced by corticotropic pituitary extract may also be associated with a virilising adrenal cortex effect (hypertrophy of the clitoris, etc.). Several authors have furthermore induced adenoma in the adrenal cortex with pituitary extract (Putnam *et al.* 1929; Anselmino *et al.* 1933, 1934, 1935).

It is true that cancer in the adrenal cortex does not seem to have been observed after injection with corticotropic pituitary extract. On the other hand, it is known that adrenal cortex tumours — with or without androgenous effect — and also adrenal cortex cancer, can be induced by gonadectomy — that is to say, the cancer, too, can be the result of an endocrine disturbance. Thus, Woolley and co-workers (1943) observed that a definite mouse race, which did not present adrenal tumours spontaneously, showed adrenal cortical cancer in great frequency $\frac{1}{2}$ a year, and regularly 1 year, after gonadectomy in males and females alike. In another race, gonadectomy led to nodous hyperplasia of the cortex. In the same way, Spiegel (1940), by castrating young guineapig males, obtained adenoma in the adrenal cortex and restitution of the accessory sex organs $2\frac{1}{2}$—4 years after the operation in 3 of about 200 animals. The control animals behaved normally. Though neither Woolley nor Spiegel advance the theory, it is obviously natural to presume that the gonadectomy affected the adrenal cortex via the hypophysis in their experiments.

STRUCTURE OF THE ANTERIOR PITUITARY LOBE AND THE CRITERIA FOR CORTICOTROPIC FUNCTION

On purely histological grounds, hyperfunction was taken to lie behind the changes in the anterior pituitary in Cushing's syndrome and in some cases of adrenal virilism — *i. e.* the hyaline change according to Crooke, and the hypertrophic amphophiles. In view of the biochemical and experimental discoveries cited above, the question arises as to whether the pituitary change found is the expression of a *corticotropic* hyperfunction. This would obviously be proved if Cushing's syndrome, where pituitary changes are observed to appear most regularly and most strongly, could be taken to involve only the mechanism of corticotropic hyperfunction of the anterior pituitary → adrenal cortex hyperfunction → clinical symptoms. However, as yet far too few cases of Cushing's syndrome have been investigated according to Jores and Beck for the first link in this genetic connection to be considered generally proved. Besides, Cushing's syndrome also presents symptoms which in all probability are contingent on other pituitary factors than the corticotropic one. Polyglobulia and osteoporosis, at any rate, are probably affected by other pituitary factors than the corticotropic, and possibly disturbances in the carbohydrate metabolism also (cf. Cushing 1932; Jores 1936, 1939; Nordenson 1944; Zondek 1944). On the other hand, it is clear that the conditions in Cushing's syndrome, where both signs of osteoporosis and polyglobulia, and disturbances in the carbohydrate metabolism, may sometimes be lacking, despite Crooke's hyaline change in the anterior pituitary lobe (cf. Bergstrand's case 1934 with Gellerstedt 1938 a, 1939), make it likely that the hyaline change really indicates corticotropic hyperfunction.

Experiments have also been made to work out the importance of the hyaline change, but the results are very unreliable. A number of authors have — probably wrongly — considered them to point to an effect from the adrenal cortex on the hypophysis. Thus Jores (1937—38 a, b) reported that, after injecting large quantities of cortydin (adrenal cortical extract),

he observed a reduction of the relative number of basophiles in the anterior pituitary lobe of rats, together with histological changes in the basophile cells, which he compares with Crooke's hyaline change. It is clear, however, that the comparison is not justified, for Jores's cells lack true hyaline fields and are characterised by loose ('aufgelockert') bodies, poorly tingible basophile granules, and vacuoles.

On the other hand, Severinghaus *et al.* (1939) has induced the hyaline change in the anterior pituitary of dogs. His experiments were complicated, however, and allow for many interpretations. Thus, on a first group of dogs, Severinghaus injected sheep pituitary extract over a long period, and on a second group, antihormone serum from dogs of the first group. In both groups the thyroid, gonads and adrenals atrophied. Similarly, the anterior pituitary lobe of both groups showed vacuolised basophiles, recalling partly castration cells and partly thyroid ectomy cells; there were also cells very like Crooke's, and large cells which Severinghaus calls 'degranulated basophiles' with a hypertrophic Golgi zone. The latter cells seem to be identical with the hypertrophic amphophiles observed together with Crooke's cells in Cushing's syndrome and adrenal virilism (cf. Graef *et al.* 1936; Gellerstedt *et al.* 1939; Mellgren 1942; Luft 1944). A third group of experiment animals consisted of sheep, which were given sheep pituitary extract. In these animals the gonads hypertrophied, but the thyroid and adrenals were not changed, and only degranulated basophiles appeared in the anterior pituitary lobe. Severinghaus interprets the results as showing that, in the dogs, the antihormone (formed in the first group, and administered in the second) lowered the pituitary functions and induced mainly degenerative changes (he reckons the Crooke's cells as such), together with secretory pictures (*i. e.* the degranulated basophiles). On the other hand, it is clear that Severinghaus's results *might* be taken to show that the antihormone reduced the function of the periphery organs; the very decrease of the peripheral hormones inhibiting the anterior pituitary lobe might cause an increase in the pituitary's secretion of glandotropic hormones, the Crooke's cells and the degranulated basophiles

then expressing a raised function (corticotropic, gonadotropic or thyrotropic).

As regards the adrenal cortex, this theory assumes that an increased function there retards the anterior pituitary lobe's secretion of corticotropic hormone, and a lowered function accelerates it. The first part of this assumption is probably correct: Ingle (1938) showed that the adrenal cortex of normal (but not of hypophysectomized) rats rapidly atrophies on the administration of large quantities of cortin, and the compensatory adrenal hypertrophy after unilateral adrenalectomy is not forthcoming if cortin is given (Ingle and Kendall 1937). The second part of the assumption is also probably correct, for compensatory adrenal hypertrophy does not occur after the removal of one adrenal gland from the hypophysectomized rat (Collip, Anderson *et al.* 1933; Schumacker *et al.* 1934). With normal compensatory hypertrophy, however, it is not clear how far a lowered consumption of corticotropic hormone plays a part.

Even if these two assumptions hold, *i. e.* if there is increased corticotropic anterior pituitary function after adrenalectomy, as in Severinghaus's experiment, the meaning of the hypophysis picture in the adrenogenital syndrome becomes no clearer: no one has ever described Crooke's cells after adrenalectomy, though lowered number of basophiles and degranulation of these cells have certainly been reported (Schumacker and Firor 1934, dog; Oka 1937, rat; Herrick *et al.* 1940, hen). Others, on the other hand, have found change in the acidophiles, but normal basophiles (Igura 1927; Lehmann 1929; Martin 1932). Human beings with Addison's disease have also been found to show degranulation of the basophiles, degenerative forms of basophiles with pyknotic nuclei and a lowered number of basophiles, but not Crooke's cells (Berblinger 1932, 1942; Crooke and Russel 1935; Romeis 1940).

Ingle's above-cited experiments with rats (1938) make it necessary also to take into account *the possibility that the anterior pituitary lobe may produce substances with an inhibiting action on the adrenal cortex*, since Ingle found that atrophy of the adrenals after large quantities of cortin only appears

in normal animals, not in hypophysectomized ones. This would seem to enable us to interpret the hyaline change and the hypertrophic amphophiles in the anterior pituitary lobe in the adrenogenital syndrome as signs of a *depressing* action on the adrenals. The connection between the anterior pituitary lobe and the adrenal cortex in the adrenogenital syndrome would then appear diametrically opposite to the one discussed above as the most plausible *a priori*: *i. e.* it would then seem that the hyperfunction of the adrenal cortex were primary, and induced the inhibiting pituitary effect, and that the histological signs of hyperfunction in the pituitary consequently indicate the intensification of a secretion of a substance depressing the adrenal function (cf. Bauer 1936, and others). It is true that this theory is not directly opposed to all the experimental observations showing that hyperplasia and adenoma of the adrenal cortex, with or without androgenous effect, *can* be induced by the pituitary corticotropic factor. On the other hand, it is difficult to use the same theory to explain why the pituitary change in Cushing's syndrome is more regular (probably obligate) than the adrenal cortex change. Above all, however, the theory of an adrenal-inhibiting pituitary function in the adrenogenital syndrome clashes direct with the observations of raised content of corticotropic factor in the blood of such cases. Even if the observations mentioned are, perhaps, not absolutely conclusive proof (see above), they nevertheless make it extremely unlikely that a pituitary function, actively depressing the adrenal cortex function, is generally characteristic of the adrenogenital syndrome.

THE PATHOGENETIC ORIGIN OF THE ADRENOGENITAL SYNDROME

Even if the connection between pituitary and adrenal cortex can be regarded established in certain, and possibly all forms of the adrenogenital syndrome, and even if it is still very likely that the pituitary disorder is primary to the adrenal disorder, this does not make the *primum movens* of the disease clear. Ross and co-workers (1941) considered gonadal failure to be primary, leading to disappearance of the inhibition on the anterior pituitary lobe. Both Spiegel's and Woolley's ex-

periments point strongly in that direction (see above). Further, in a eunuchoid, the present author (1942) observed changes in the anterior pituitary which had a certain resemblance to those in Cushing's syndrome, and at the same time weakly positive PFR in the adrenal cortex. These observations do not, however, agree very well with those made earlier in eunuchoids and castrates (cf. Altmann 1930; Romeis 1940). Furthermore, Anderson and co-workers (1943) maintain that a gonadal genesis of this kind can hardly explain the cases of prepubertal virilism. Moreover, it is known that the adrenogenital syndrome may occur in adults without perceptible testicular or ovarian changes (see above).

Kraus's (1934) idea that the disease is ultimately due to a general metabolic derangement, which induces the changes in the endocrine organs, is obviously improbable; it has been subsequently revised by Kraus himself (1937 b). As increased cerebral pressure may occur with increased weight of the pituitary and hyperplasia of the adrenal cortex (without the clinical adrenogenital syndrome), and as different processes in the pituitary-hypothalamic system may lead to dystrophia adiposo genitalis, sometimes together with enlarged adrenal cortex, several authors have calculated that disturbances in the midbrain induce the adrenogenital syndrome via the pituitary (cf. Kraus 1937). Several experiments on animals might point in the same direction (cf. above, Smith 1923). On the other hand, it is known that the pituitary corticotropic function, unlike its gonadotropic and thyrotropic functions, may proceed extensively, independent of the connection with the midbrain, at any rate in rats (P. E. Smith 1930; Westman and Jacobsohn 1937; Westman 1940; Westman and Jacobsohn 1940; Uotila 1940; Anselmino and Hoffmann 1941; Berblinger 1942; Hillarp and Jacobsohn 1943). Thus, no definite conclusions can at present be drawn as to the factors which may possibly be thought to govern the pituitary and adrenal disturbances in the adrenogenital syndrome.

2. MENOPAUSAL SYNDROMES

The designation of menopausal syndromes is used in the following pages to denote two syndromes occurring in exceptional cases in men and younger women, but usual in old women, namely 'Cushingoid habitus', and Syndroma Morgagni. The former can be defined as hirsutism, usually only in the face, with obesity of more or less distinct 'buffalo type'. Syndroma Morgagni implies the same picture in combination with hyperostosis frontalis interna.

CUSHINGOID HABITUS

The concurrent appearance of hirsutism and obesity was advanced by Achard and Thiers 1921 as a particular syndrome, common in women in the menopause or after ovarectomy. They also pointed out the external likeness between this menopausal syndrome and pronounced virilism of the form nowadays acknowledged to be adrenal. Achard and Thiers were particularly interested in the occurrence of diabetes in these patients, however, and discovered that diabetes was an inconstant and not particularly common symptom in 'les femmes à barbe'. They contributed a case of their own, in which they had established slightly hypertrophic adrenals.

On the basis of similar observations, Berblinger (1928) assumed that a beard in the aging woman was due to the predominant influence of the adrenal cortex on the contrasexual sex characters, when the ovarian function became weaker.

The external likeness between the menopausal syndrome of obesity and hirsutism on the one hand, and adrenal virilism in younger women on the other, also prompted Broster and co-workers (1933, 1934, 1938, 1944) to regard this menopausal syndrome as a form of the adrenogenital syndrome, 'the postmenopausal virilism'. They performed unilateral adrenalectomy on one such case, but without any real effect on the disease picture. After Cushing's work of 1932, the old women with beards and obesity were regarded on the same grounds as a milder form of Cushing's disease, a 'Cushingoid habitus', parti-

cularly as the obesity in these old women often took the 'buffalo type' (Raab 1936; Kosmola 1936; Gellerstedt *et al.* 1939).

However, there is no reliable anatomical background for a conception of this kind. The hypertrophy of the adrenals, reported by Achard and Thiers (1921), and others, refers to single cases. The size of the adrenal cortex varies considerably even when normal, and in different pathological states (cf. Kolde 1913; Kaplan 1932—33; von Lucadou 1935—36; Kraus, *cit.* Berblinger 1942; Materna 1942; Liebegott 1944); a systematic investigation would therefore be required to establish a possible adrenal hyperplasia in the old fat and bearded women. Vines (Broster *et al.* 1938) admittedly assumed that the weakly positive PFR which he, as subsequently Sudds (1940), observed in old women might have to do with the post-climacteric hypertrichosis, but he did not investigate this correlation further. A certain support for Vines's theory was nevertheless provided by the present author (1942), who found weakly positive PFR in the adrenal cortex in 3 of 5 cases with 'Cushingoid habitus', but only in 1 of 4 cases without endocrine characters.

Earlier data are unreliable on the anatomy of the hypophysis in 'Cushingoid habitus', also. Gellerstedt (1939) assumed that the increased frequency shown by aging persons in the basophile cells of the anterior pituitary lobe (cf. Rasmussen 1929, 1933) might be the anatomical expression of an 'atoxic' basophile hyperfunction, which induced 'Cushingoid habitus' in the same way as its 'toxic' counterpart, visible as the hyaline change, induces Cushing's disease. However, it still remains to prove that the supposed increase of basophiles really is correlated with the 'Cushingoid habitus', and is not merely a general phenomenon of age. Crooke's (1935) and Ecker's (1938) finding of hyaline change in isolated 'normal cases' may similarly be thought to have to do with mild forms of the adrenogenital syndrome, for the present author (1942) found hypertrophic amphophiles and hyaline basophiles in the anterior pituitary more often in women with 'Cushingoid habitus' than in control cases. However, the material consisted of only 10 cases, and the cell frequencies in the pituitary were not est-

ablished quantitatively with a differential count, so that the results must be regarded as uncertain (cf. Rasmussen 1929, 1936).

Summing up, it can be said of the 'Cushingoid habitus' that the external likeness to Cushing's syndrome is not borne out by any established patho-anatomical background.

SYNDROMA MORGAGNI

Henschen showed (1936, 1937, 1938, 1944) that the triad obesity, hirsutism of male type (specially in the face), and characteristic gyrated hyperostoses on the inner side of the ossa frontalia form a uniform syndrome, which he called Syndroma Morgagni after its first observer (Morgagni 1761). As this triad is most often found in women after the climacteric, it can be regarded as a variant of the menopausal 'Cushingoid habitus', particularly as the frontal hyperostoses — *i. e.* Syndroma Morgagni's special symptom — vary in size from case to case, and are usually quite small (Henschen 1937, 1944; cf. also Moore 1935, 1936; Jacobsen and Nielsen 1942; Louw 1943).

Clinical aspects. The recent extensive literature on Syndroma Morgagni deals particularly with its frequency and clinical importance (cf. Campos 1943 and Henschen 1944). The data as to the frequency of frontal enostoses are very varied, probably because most investigators base themselves on roentgen examinations or on quite small autopsy materials of different origin (Moore 1935, 1936; Lucherini 1939; Jacobsen and Nielsen 1942; Henschen 1944). However, Henschen has unmistakably shown that Syndroma Morgagni is common in old women but rare in men (1944), finding, in an autopsy material of 1000 women and 700 men, frontal enostoses 100 times more often in the former than in the latter. The women showed large frontal enostoses to about 11 %, and when even the smallest were counted, the frequency was about 40 %. The frequency curve rose from 0 in the ages 30—35 years, to the maximum of about 50 % in the ages over 70 years. Furthermore, about half the cases with frontal enostoses showed a

complete Syndroma Morgagni, and only 12 % lacked both obesity and hirsutism. There was a strongly positive correlation between the three Morgagni symptoms in the whole of Henschen's material. Actually, Henschen also showed that Syndroma Morgagni is commoner than 'Cushingoid habitus' alone: he found in his entire material of 1700 cases (women + men) 126 cases of Syndroma Morgagni and 93 of 'Cushingoid habitus' (these last including a few cases of Cushing's disease), and in addition 143 cases of defective Syndroma Morgagni, *i. e.* frontal hyperostoses by themselves, or combined with only obesity or only hirsutism.

Opinions differ as to the occurrence and importance of other symptoms than obesity and hirsutism in combination with frontal enostoses (cf. surveys by Morel 1930; Henschen 1937, 1944; Campos 1943). However, Henschen has shown (1936, 1937, 1944) that Syndroma Morgagni often appears without other symptoms than those covered by the triad. The neurological symptoms in particular, already associated genetically with frontal enostoses by Stewart (1927—28) and Morel (1930, 1937), must be denoted temporary or secondary complications (Henschen 1937, 1944; Mellgren 1942). The question as to whether Syndroma Morgagni has an endocrine genesis is, on the other hand, taken further by studying the combination of the triad or the enostoses with certain other symptoms, also belonging to Cushing's syndrome. Thus, Henschen (1944) found osteoporosis in 42.2 % of the cases with enostoses, but in only 28.1 % of those without enostoses. Furthermore, hypogenitalism has not infrequently been observed even with frontal enostoses in men (Lucherini 1939; Möller 1942, and others; cf. also Campos 1943 and Henschen 1944), though not regularly (Henschen 1937). In the same way, hypertonia has often been reported with Syndroma Morgagni, but in other cases the blood pressure was normal. Henschen (1944) has made it likely that the weight of the heart in Syndroma Morgagni is greater than in fat women as a whole. As regards the connection between Syndroma Morgagni and diabetes mellitus, finally, it is well known that diabetes is usual in old, fat persons. Bartelheimer, who made a special study of the occurrence of extrapancreatic

symptoms among diabetics (1939 a, b, c, d; 1940 a, b), found that 'Cushingoid habitus' and Syndroma Morgagni were very usual in diabetes refractory to insulin. On the other hand, Henschen, who already in 1937 advanced the relatively great frequency of diabetes in Syndroma Morgagni, found in 1944 that his large autopsy material did not show any positive correlation between diabetes on the one hand, and the separate Morgagni symptoms of enostoses or hirsutism on the other. However, he did not investigate the possible connection between diabetes and adiposity of the 'buffalo type'.

Thus, it is plain that Syndroma Morgagni has more in common with Cushing's disease than merely the external habitus. And, indeed, this was maintained by Henschen already in 1937, and also confirmed by the cases of Cushing type with frontal enostoses which have been described by Bartelheimer (1939 c). Important support to the assumption that the likeness embraces an increased corticotropic pituitary function was given by Bartelheimer and Cabeza in 1942. Using Jores's method (see above, concerning pronounced forms of the adrenogenital syndrome), these investigators found an increased quantity of the corticotropic factor in the blood of 10 of 12 cases of 'Cushingoid' type — some of them nevertheless complete Cushing's syndromes — and in the only case of Morgagni type thus investigated. It is furthermore interesting that Bartelheimer and Cabeza admittedly found positive correlation between corticotropic blood factor and obesity + diabetes, but not between this factor and hypertonia + diabetes. The latter observation would seem to oppose that of Jores (1936), who found an increase of the blood's corticotropic factor in 21 of 28 patients with genuine hypertension. However, Jores did not investigate the distribution between obese and non-obese cases with hypertension.

The position of Syndroma Morgagni as a typical menopausal phenomenon is hardly shaken by the fact that the syndrome has, in isolated cases, been observed in young women and in men also (Iversen 1942; Kirk 1942; Andersen 1942, and others; cf. also Campos 1943, and Henschen 1944). The kinship of the syndrome with Cushing's syndrome is in the same way unshaken

by the fact that frontal enostoses are not strictly specific to the 'Cushingoid' syndrome, but have in some cases been observed in association with pregnancy (Leszler 1940; cf. Henschen 1944), in acromegalia, and in other endocrine disease pictures (Holten 1943; Henschen 1944).

Anatomical aspects. Despite the abundant literature on the clinical aspects in Syndroma Morgagni, anatomical investigations of the endocrine organs have been performed only in a few cases of the syndrome.

Stewart (1927—28) found 3 insane women with obesity of the pituitary type and frontal enostoses to show changes in the anterior pituitary lobe, namely sclerosis and deficiency of the chromophile elements; in 2 of the cases the acidophiles were fairly numerous, however. From this Stewart was the first to draw the conclusion that 'we are here dealing with a hitherto undifferentiated type of dyspituitarism'. Morel (1930), who examined the hypophyses in 5 of 17 old women with frontal enostoses, found 1 case to show a large chromophobe adenoma (case 8); in 3 cases (1, 3, and 4) the acidophile cells preponderated, in 2 cases (1 and 4) the basophiles were scarce, and in 2 cases (3 and 4) the chromophobes were scarce. In 1 case (2) there was sclerosis of the anterior pituitary. In a larger material of Syndroma Morgagni, Henschen (1937) found an almost constant, often strong increase of the number of acidophile and basophile cells in the anterior pituitary, in combination with a great frequency decrease of the chromophobes. Ritter (1938) reported a case of Syndroma Morgagni with great increase of the number of basophiles in the anterior pituitary. The value of all these quantitative hypophysis findings is uncertain, however, since they are not established with quantitative methods such as a differential count (cf. Rasmussen 1929, and Campos 1943). Using the comparison microscope, the present author (1942) found no perceptible differences in the frequency of the basophiles, the acidophiles and the chromophobes between 7 cases of Syndroma Morgagni and 5 control cases of old women of corresponding ages. The same result was reached by Floderus (1944), who examined 3 anterior

pituitaries from women with Syndroma Morgagni and 5 control cases with a differential count, and besides these 5 Morgagni cases with ordinary methods. On the other hand, Reider (1937, 1938) found a 55-year-old sterile woman with frontal enostoses to show qualitative pituitary changes, namely hypertrophic amphophiles and enlarged basophiles. Reider's observation tallies well with those which the present author made in 1942 on the above-mentioned material, since this presented hypertrophic amphophiles more often and in greater abundance in Syndroma Morgagni — as in 'Cushingoid habitus' — than in the control cases. Before these changes can be accepted as essential to the menopausal syndromes, however, they must be substantiated by a differential count on a larger material (cf. above).

Degenerative changes round about the third ventricle, above all in the posterior hypothalamus region, were observed by Morel (1930) in 4 cases of frontal enostoses (the above-cited cases 1—4). The importance of this and similar findings (Ritter 1938) is nevertheless made uncertain by the mere localisation of the changes (Campos 1943), and particularly so because Henschen (1937) made similar observations not only in Syndroma Morgagni but also in control materials of old women without enostoses.

Data as to the other endocrine organs in Syndroma Morgagni are even more scanty. Most investigators have not been able to discover any characteristic or noteworthy changes (Bonnamour and Jamin 1926; Morel 1930; Henschen 1937; Korpássy 1939; Andrews 1942; Campos 1943). It is particularly interesting that Henschen (1937), who has probably investigated the largest material of Syndroma Morgagni, did not find any adrenal hyperplasia or adrenal cortical adenomas in cases with strong facial hirsutism. The ovaries in his cases showed the usual picture of senile atrophy and sclerosis. The present author found the PFR positive in the adrenal cortex of one case, and weakly positive in one case, of Syndroma Morgagni. However, the same comment holds for these results as for those in 'Cushingoid habitus'; that is to say, only a systematic investigation on a larger material, with corresponding

material for comparison, can decide whether the endocrine organs show characteristic changes or not.

Summing up, then, 'Cushingoid habitus' and Syndroma Morgagni can, in women, be regarded as typical menopausal syndromes, which bear not only morphological clinical resemblances to the adrenogenital syndrome, particularly to Cushing's disease. That is to say, the finding of an increased quantity of the corticotropic factor in the blood of cases from all the categories mentioned make it likely that an increased corticotropic pituitary function and secondarily raised adrenal cortex function may be common to them all. On the other hand, no characteristic changes in pituitary or adrenal cortex have been established in the menopausal syndromes. The anatomical similarities between the menopausal syndromes and the adrenogenital syndrome, which the present author claimed to find in 1942 for pituitary and adrenals, need confirmation.

3. PROSTATIC HYPERTROPHY

The question as to whether the so-called prostatic hypertrophy is an expression of an endocrine disturbance has been much discussed. As, of all endocrine organs, the testis is the one which unquestionably has the most perceptible directly stimulating effect on the accessory sex glands, the discussion as to the endocrine genesis of prostatic hypertrophy has almost exclusively regarded the function of the testis. However, we now know that the adrenal cortex can produce substances having the action of all the known sex hormones (see above). There is therefore reason to investigate how far an increased function of the adrenal cortex may be the cause of prostatic hypertrophy.

THE TESTIS THEORIES

At present there are two hormonal theories as to the genesis of prostatic hypertrophy; for their background see Törnblom's excellent work of 1942. One builds on the fact that both androgens and oestrogens are present in the male organism. As the man gets older, the testis gradually atrophies, and its

androgen production falls. A relative preponderance of oestrogens thus arises in the blood, and this affects the prostate, with prostatic hypertrophy as a result. It has been advanced, in special support of this theory, that the periurethral tissues from which prostatic hypertrophy originates, derive from 'Müllers Hügel', and is therefore of bisexual nature (Moszkowicz 1932; Vidgoff 1939; Minder 1942). In his account of the literature, Törnblom has shown this theory to have many weaknesses.

The other theory builds on the assumption that the testis secretes both testosterone, formed by the interstitial cells, and another hormone, formed by the germinal tissue and with an inhibiting action on the pituitary. The germinative tissue in the aging man atrophies, so that the hypophysis secretes more gonadotropin and the testosterone secretion of the testis is raised, with prostatic hypertrophy as a result. Using rats, Törnblom (1942) showed that the testicular germinal tissue really does secrete a hormone of its own. The same result was reached, independently of Törnblom, by Joël (1942). However, Törnblom went further, and showed that this hormone had an inhibiting action on the anterior pituitary of rats, since by selective destruction of the testicular germinal tissue, he induced an increase of weight in both prostate and the seminal vesicles, and in the anterior pituitary, as well as castration cells in the latter. He assumed that the growth of the accessory sex organs was started by an increased production, via the hypophysis, of the testis hormones formed in the interstitial cells. He was furthermore able to replace the action of the destroyed germinal tissue with oestrogens, and show that the inhibiting hormone probably consisted of oestradiol.

Although the physiological background for the 'second theory' is thus established, it has certain weaknesses. In further investigations Törnblom has determined the weight of the seminal vesicles and prostate in men of different ages, proceeding from the conception that if the greater prostate weight in older men were due to an increased testosterone action, then the vesicles should also become heavier (in conformity with the well-known equal effect of testosterone on prostate and vesicles

in animals). This, however, was not the case (investigations to be published; personal communication to the present author). A further argument against the 'second testis theory' is that most investigators have found a lowered or normal excretion of urine androgens in old men and in such as have prostatic hypertrophy (cf. Törnblom 1942; Miller 1942; Miller and Moore 1942). Furthermore, using a special method, Törnblom has found the concentration of comb-growth-promoting substances in the blood of men with prostatic hypertrophy to be equal with that of normal men (personal communication to the present author; to be published).

AN ADRENAL THEORY

Thus, there are two circumstances found in men with prostatic hypertrophy which argue against prostatic hypertrophy being ultimately induced by increased function of the interstitial cells of the testis: 1) that prostatic hypertrophy is not accompanied by hypertrophy of the seminal vesicles, and 2) that androgenous substances have not been demonstrable in increased quantity. On the other hand, it seems not unlikely that both circumstances might be explained if, instead of an increased interstitial cell function in the testis, we imagine an increased function of the adrenal cortex, set up via the hypophysis as a result of atrophy of the testicular germinal tissue — a theory which would thus not clash with any of the arguments advanced in favour of the testis theories (cf. Vidgoff 1939 and Törnblom with the biochemical and experimental data under 'adrenogenital syndrome' above). Strong support to this theory is provided by Davidson's (1937) observation that corticotropic pituitary extract in hypophysectomized rats has a far greater growth-stimulating action on the prostate than on the seminal vesicles. In other words, it is possible that the relative low weight of the vesicles in enlargement of the human prostate according to Törnblom is due to a hyperfunction of the adrenal cortex. The recently mentioned contradictory, and mostly negative, results of hormone assays on urine from men with prostatic hypertrophy might point in the same direction. In any case they do not rule out

an adrenal hyperfunction, as even in certain cases of adrenal virilism, hormone assays on urine androgens have sometimes had a negative result (cf. above). Particularly interesting, also, is a case of prostatic hypertrophy reported by Deming and co-workers in 1935, namely a 74-year-old man with atrophic testes, which had probably been incapable of any function since his early twenties. Unfortunately, the report does not say whether the testes were wholly without interstitial cells. In spite of this, and even if this is an extreme exception, it nevertheless shows that if prostatic hypertrophy is due to a hormone surplus at all, this hormone can in all probability be secreted by another organ than the testis. In view of Spiegel's (1940) castration experiments on guineapigs (see above), it seems very likely that, in Deming's case, this other organ is the adrenal cortex.

ANATOMY OF THE ENDOCRINE ORGANS

Systematic anatomical investigations of the endocrine organs in prostatic hypertrophy have only been performed in small numbers, and with meagre results. Thus, Teem (1935) was unable to show any anatomical correlation between the testicular interstitial cells and prostatic hypertrophy. Jones (1939 a, b) investigated the prostate and hypophysis of 270 autopsy cases, of whom 168 had not, and 102 had subclinical adenomas of the anterior pituitary. He found a somewhat higher frequency of prostatic enlargement in the latter group (47.0 %, to 30.4 % in the former). As, however, the frequency of prostatic hypertrophy was not significantly greater in any one type of pituitary adenoma, Jones concluded that his investigation results merely expressed the innate tendency towards overgrowth of tissue in certain persons. A further 33 cases with 'clinical' pituitary adenomas (7 of acromegaly, 12 of hypopituitarism, 5 of obesity and 9 of only pressure symptoms) presented no great frequency of prostatic hypertrophy. On the other hand, atrophy of the prostate gland was found in cases of considerable pressure atrophy of the pituitary, due to large tumours. In the 168 cases without pituitary adenoma, Jones also investigated the approximate frequency of acidophiles,

basophiles and chromophobes in the anterior pituitary, acini in the pars intermedia, and the infiltration of basophile cells in the pars nervosa. He found no correlation between any of these factors and the size of the prostate. It is hardly necessary to repeat that as uncertain an observation as this last must be considered to be due to the rough method of investigating the hypophysis.

No systematic investigations seem to have been made into the anatomy of the adrenal cortex in prostatic enlargement.

Summing up, then, certain clinical and biological observations can be interpreted in favour of an adrenal cortical hyperfunction as the cause of prostatic hypertrophy. The supposed adrenal hyperfunction might possibly be induced via the hypophysis following decreased oestrogen production from the testicular germinal tissue. However, this theory is still insecurely founded, and has no anatomical background. It seems worth trying out, however, particularly in view of the fact that prostatic hypertrophy is possibly an analogous phenomenon to the menopausal syndromes in women.

CHAPTER III

PROBLEMS

Proceeding from the survey of the literature, and in particular in view of the findings reported by the present author in 1942, the following questions can be drawn up:

1. Is the anterior pituitary lobe in adrenal virilism regularly characterised by the same elements as in Cushing's disease, *i. e.* hyaline basophiles and hypertrophic amphophiles?
2. Is a corresponding pituitary change also characteristic of the menopausal syndromes (Syndroma Morgagni and 'Cushingoid habitus')?
3. Is a corresponding pituitary change also characteristic of prostatic hypertrophy?

If these questions can be answered affirmatively, we then have the problem of the importance of the change observed. The groups 'adrenogenital syndrome', 'the menopausal syndromes' and 'prostatic hypertrophy' have been chosen for investigation, as there were various reasons — besides the structure of the hypophysis — for assuming that they were all characterised by an increased corticotropic pituitary function. To see whether the pituitary change observed does express a corticotropic function of this kind, one can, with morphological methods, both analyse the pituitary picture cytologically, and investigate the correlations of the picture with possible changes in other endocrine organs, particularly those in the adrenal cortex.

The cytological analysis offers nothing new in as much as the histological characters of the hyaline basophiles and the hypertrophic amphophiles (hereafter collectively denoted 'the special cells') have been discussed in detail earlier on. It is known that the structure of these cells indicates an enhanced

function. On the other hand, it remains to confirm the assumption that the special cells are pathological functional stages of basophiles, particularly in view of the experimental results which point to the basophile granules as carriers of the corticotropic factor. It should be obvious that the hyaline change expresses a special function of the basophile cells. The same conclusion is probably applicable to the hypertrophic amphophiles, thanks to the observation of transitional forms between these latter and normal and hyaline basophiles. This needs confirmation. Furthermore, the indication of the hypertrophic amphophiles' origin can be sought by investigating their topographical connection with other types of pituitary cells. — Finally, there is the question as to whether the special cells express a function of pathological nature (dysfunction), *i. e.* express incretion of a hormone not normally present. The idea of such a dysfunction receives morphological support only by the observation that the morphology of the anterior pituitary lobe in the unquestionably pathological conditions (the adrenogenital syndrome) differs specifically and not merely qualitatively from that in corresponding constitutional variants (menopausal syndromes), and from that in persons with fully normal endocrines.

These considerations have given rise to these further questions:

4. Is there a regular occurrence of transitional forms between the special cells among themselves, and between these cells and normal basophiles?

5. Are the hypertrophic amphophiles topographically correlated with another given cell type in the anterior pituitary lobe?

6. Is there a difference of kind, or only a difference of degree, between the structure of the hypophysis in the three groups 'adrenogenital syndrome', 'menopausal syndromes' and 'endocrinely normal persons'?

Finally, to study the connection between the structure of the hypophysis and changes in other endocrine organs, the following main question has been drawn up:

7. Is there any correlation between a definite pituitary structure (above all the frequency of the special cells) and any change in the size or structure of the adrenal cortex, indicating enhanced function in the latter (first and foremost the PFR) in a material covering the adrenogenital syndrome, menopausal syndromes, prostatic hypertrophy, and persons with normal endocrines? If this is so, it remains to investigate the cause of the correlation, *i. e.* to seek an answer to question

8. Is the change in the adrenal cortex due to the pituitary change, or *vice versa,* or are both factors governed by a third? In view of the last-mentioned possibility, the same material will be investigated to see whether the pituitary change is also correlated with the weight or structure of any other endocrine organ than the adrenal cortex.

CHAPTER IV

MATERIAL AND METHODS

1. MATERIAL

The material consists of the endocrine organs (hypophysis, epiphysis, thyroid, parathyroids, adrenals, pancreas and gonads; in some cases, the thymus also) from 261 autopsy cases, divided into 3 groups.[1] The first of these, the main material, comprises a comparison material of 'endocrinely normal' women, men and children, cases of menopausal syndromes and prostatic hypertrophy. The second group consists of 16 cases of the adrenogenital syndrome, *i. e.* pronounced adrenal virilism (of which there are 6 typical cases and 1 uncertain case) and Cushing's disease (9 cases). The third group, finally, contains 6 cases of diabetes (not combined with menopausal symptoms or prostatic hypertrophy), 2 cases with parathyroid hyperfunction, 2 with eunuchoidism and 2 with Addison's disease. This last group has been investigated to ascertain the specificity of the histological picture of the hypophysis in the adrenogenital syndrome, the menopausal syndromes and prostatic hypertrophy. Case reports for the second and third groups will be given in connection with the results in Chapter V. It remains here to describe the first group in more detail.

THE MAIN MATERIAL

The distribution of the cases within the main material is shown in table 1.[2]

[1] The material includes the cases published by the present author in 1942.

[2] Case reports for the same material, covering identification number, main diagnosis and the most important results of individual examinations have been placed in the University libraries of Upsala and Lund, and in the library of the Karolinska Institute in Stockholm.

Table 1. Main material. Nature and grouping of the cases.

Nature of the cases	Number of cases with the endocrine organs				Age in years, mean
	Histologically examined		Only weighed	Total	
	Diff. count of hypophysis made	Diff. count of hypophysis not made			
Endocrinely normal women before the menopause. 16—46 years	14	9	3	26	28.8
Endocrinely normal women in the menopause. 41—99 years	15	14	23	52	66.4
Endocrinely normal men 18—48 years	7	5	10	22	37.2
Endocrinely normal men 50—84 years	12	8	25	45	63.1
Endocrinely normal children 10 ♂ + 5 ♀. 1 day—9 years	6	0	9	15	—
Menopausal syndromes, ♀ 42—93 years. Includ. 1 ♂ with Syndr. Morg. . .	18	26	1	45	65.9
Prostatic hypertrophy 51—88 years	12	6	10	28	73.1
Total	84	68	81	233	—

The choice of cases. The 'endocrinely normal'. The cases have been chosen on the clinical data, the external habitus at the autopsy, the macroscopic anatomy of the calvaria (presence or absence of frontal enostoses) and the macroscopic anatomy of the prostate (presence or absence of adenomatous hyperplasia). Thus, none of the 'endocrinely normal' cases have shown clinical signs of endocrine disease. All were submitted to a routine clinical examination except 5 who had all died suddenly; these latter were a 26-year-old woman from submersio, a 22-year-old woman from congelatio pedis bil. et pneumonia acuta (differential count of hypophysis, R. M., Sö. 20. 12. 43), a 24-year-old man who had had an accident, multiple fractures and fat embolisms, a 26-year-old man in military service with infection of the upper respiratory tract and cause of death uncertain, and a 51-year-old man with fibrosis myo-

cardii et stasis organorum (differential count of hypophysis, O. 150/44).

To call the fertile women normal, a normal menstruation cycle should be an additional requirement in each case. As only a small autopsy material of this kind has been available, the group of 'endocrinely normal women before the menopause' have been put together as follows. Of the 14 cases with a differential count of the hypophysis, 6 had had a regular menstrual cycle and the date of the last menstruation was known. The interval between this date and death was established as agreeing with the histological picture of the uterus mucosa at the autopsy. There was agreement of this kind in a further 2 cases, but the earlier menses had not been registered. These 8 cases must be considered sexually normal. A further 3 cases (O. 19/43, aged 34 years, with glioma cerebri; 26/43, 25 years, with pulmonary tuberculosis; 139/43, 27 years, with haemorrhagic pneumonia) were probably normal, as the histological pictures of the ovaries and the uterus mucosa were normal, and agreed with one another; however, there are no data for the last menses in any of the 3 cases, and only in 1 case (O. 19/43) had the earlier cycle (regular) been registered. In 1 case, moreover (O. 333/43, 26 years, glomerulonephritis chron.), the menstrual cycle had previously been regular, but had probably given place to amenorrhoea in the last few months before death. The ovaries had no corpora lutea, and the uterus mucosa was low and regular, recalling the proliferation phase, though with a somewhat fibrous stroma. In the 2 last cases, finally (O. 408/42, 25 years, and 168/44, 17 years), there was an unquestionable delayed or arrested menstrual rhythm, for though the interval between the last menstruation and death was 3—4 weeks, the uterus mucosa most resembled the early proliferation phase. — There were no data as to the cycle for the 12 young women without a differential count of the hypophysis (see table 1). Judging from the histology of the ovaries and the uterus mucosa, it is likely that at least 7 had menstrual disturbances resembling the 3 last-named cases in the previous group.

The investigation of the external habitus has paid special

attention to the amount and distribution of the subcutaneous fat, the external genitals, and growths of hair. Obesity of plain or suggested 'buffalo type' (hypophyseal type) is one of the symptoms in the menopausal syndromes. To get an all-round comparison material, it has been recruited not only from lean individuals but also from such as have normal or abundant flesh with the customary distribution (not 'buffalo type'). The composition of the material in this respect is seen in table 2.

Table 2. Main material, adults. Occurrence of obesity.
The smaller raised figures give cases with diff. count of hypophysis made.

Nature of the cases	Number of cases			
	Fat	With normal flesh	Thin	Total
Endocrinely normal women before the menopause	1^{1}	12^{8}	13^{5}	26^{14}
Endocrinely normal women in the menopause	17^{4}	11^{6}	24^{5}	52^{15}
Endocrinely normal men 18—48 years	5^{2}	7^{3}	10^{2}	22^{7}
Endocrinely normal men 50—84 years	9^{3}	20^{6}	16^{3}	45^{12}
Menopausal syndromes (incl. 1 ♂) (Data as to flesh lacking in 4 cases)	26^{12}	3^{2}	12^{4}	41^{18}
Prostatic hypertrophy	7^{3}	10^{5}	11^{4}	28^{12}
Total	65^{25}	63^{30}	86^{23}	214^{78}

In the normal material the external genital organs are normal throughout. Growths of hair have been checked up as normal in all the women. However, one of the young women in the control material had an indefinite upper boundary to the pubes (O. 467/43), and two older women showed very slightly more hair than normal on the upper lip or chin. Further, the absence of frontal enostoses at the autopsy was established in all the 'endocrinely normal'; for 2 young women no investigation was made, however (O. 408/42, 25 years, differential count of hypophysis, and O. 196/43, 37 years, no differential count of hypophysis); in 3 old men and 3 old women (no differential count of hypophysis) the registration was in-

complete, too, but there had probably been no enostoses in any of these 6 cases.

For the composition of the material of normal children, see Chapter V.

Characteristics of the pathological groups. The boundary-line between men with and without prostatic hypertrophy has been so drawn as to include only cases with distinct adenomatous enlargement of the prostatic gland in the former category, and only cases with a gland of normal size and without adenoma in the latter.[1] It should, however, be noted that the normal cases included 3 where it had been doubtful whether the prostate was of normal size, or whether it was slightly enlarged (O. 465/43, 52 years; O. 15/44, 58 years; O. 29/44, 77 years). If there was any enlargement of the prostate in these 3 cases, it was certainly slight compared with that in the group 'prostatic hypertrophy'. Further, there was prostatic cancer in 2 cases, one with a perceptibly enlarged adenomatous gland (O. 5/44, 78 years, referred to the hypertrophy group), the other with a normal-sized and non-adenomatous gland (O. 50/44, 73 years, referred to the normal group). None of the cases mentioned separately have been used for the differential count of the hypophysis.

The cases with menopausal symptoms are grouped in table 3. In this group, 'enostoses' denote unmistakable frontal enostoses with typical structure and position, 'hypertrichosis' implies pronounced facial hypertrichosis of male type; 'obesity' implies obesity of more or less distinct 'buffalo type'. As it is difficult to make a clear distinction between this type and other forms of obesity, no case with obesity only has been included among the 'menopausal syndromes'.

[1] The weight of the prostate has not been determined, as the cases with prostatic hypertrophy were removed from the normal material at a late stage of the investigation, namely, when they had proved to be distinguished by a cellular composition of the anterior pituitary lobe, differing quantitatively from that of the remaining normal material. The boundary-line between normal men and those with prostatic hypertrophy has been subsequently made clear by excluding some cases because they were indeterminate as regards the occurrence of prostatic hypertrophy.

Table 3. The material of 'the menopausal syndromes'.

In the column 'diff. count of hypophysis not made' 4 cases without data as to flesh are lacking, namely 1 with hypertrichosis and 3 with enostoses.

Main symptoms	Number of cases		
	Diff. count of hypophysis made	Diff. count of hypophysis not made	Total
Enostoses only	3[1]	1	4
Hypertrichosis only	1[2]	8	9
Enostoses + hypertrichosis . .	2	0	2
Enostoses + obesity	4	1	5
Hypertrichosis + obesity = 'Cushingoid habitus'	2	6	8
Enostoses + hypertrichosis + obesity = Complete Syndroma Morgagni	6	7	13
Total	18	23	41

[1] Of these one man, O. 14/44, 45 years, flesh normal, diabetes mell.

[2] Also slight hypertrophy of clitoris.

The occurrence of two other symptoms which have been considered typical of the menopausal syndromes is also interesting in this connection; these symptoms are diabetes and hypertonia (see above, survey of the literature). Diabetes occurred in 5 cases of 41 with menopausal syndromes (4 without data), and in about the same proportion, *i. e.* 2 of 18, among those with a differential count of the hypophysis, *i. e.* in about 12 %. A comparison with Henschen's findings on a large corresponding material (Henschen 1944, 14—18 % diabetes), shows that the selection presented here may be regarded as representative. The cases with prostatic hypertrophy included 2 with diabetes, both in the group with a differential count of the hypophysis. The control cases of the main material do not include such as have diabetes: control cases of this kind have been grouped with other endocrine diseases in a special category (see Chap. V).

The blood pressure has, it is true, been registered in most of the clinically investigated cases, but the results are very often misleading, because many patients in this material were not examined until they had reached the stage of terminal

circulatory insufficiency. To assess the occurrence of essential hypertonia, therefore, the weight of the heart has been taken instead of the blood pressure, excluding cases with vitium organicum cordis or glomerulonephritis. Under these conditions, the weight of the heart (mean with standard error) in the group with menopausal symptoms was 380 ± 19.0 gm (determined on 33 cases), and in those of the same group who had been used for a differential count of the hypophysis it was 375 gm (16 cases). In the corresponding normal material of old women the weight was 350 ± 18.0 gm (46 cases) and 376 gm (14 cases) respectively. Thus, there was complete agreement between the groups used for the differential count, and also statistically good agreement between the groups as a whole. Among the men with prostatic hypertrophy, the weight of the heart was 466 ± 23.3 gm (26 cases), and of these, those where the differential count of the hypophysis had been made showed a weight of 465 gm. In the corresponding normal material the weights were 426 ± 24.7 gm (37 cases) and 465 gm (11 cases) respectively, *i. e.* the same agreement as among the women. It is therefore out of the question that hypertonia is over-represented in those parts of the pathological groups taken for the differential count. It is furthermore unlikely that hypertonia is over-represented in the whole of the pathological groups, for if it is not due to chance that the means for the cardiac weight in the last-mentioned groups are somewhat higher than those in the normal material, it should be possible to explain them by the greater frequency of obesity among the pathological cases (cf. table 2). This, as also the age distribution (cf. table 1), will be discussed more fully in connection with the results.

2. METHODS

In the main material (see table 1), the endocrine organs have been weighed and examined anatomically and histologically in the manner to be described below. At the beginning of the investigation, however, it was usual to take only the hypophysis and adrenals, and no weighing was done. In due

course the investigation was extended to include weighing and histological examination of all endocrine organs. Further, a number of organs have been damaged at random during the autopsy, or while being prepared. To level out the lack of weight data in those cases collected at the beginning of the investigation, a series of cases have finally been collected where *only* the weight of the endocrine organs has been determined. The material is therefore heterogeneous. However, this should scarcely affect the present problems: the choice of the factors (weight of organs, histological examination, differential count of the hypophysis) which have been determined in the individual case has been made solely on the principle that, in one and the same group of cases (*e. g.* cases of menopausal syndromes), every separate factor should be determined on a material which is similar to the group as a whole.

The separate factors have been determined as follows.

The Hypophysis

The hypophysis was removed together with the immediately surrounding bone capsule, and fixed in 10 % formalin for about 10 days. The organ was then taken out of the sella and freed from the remains of the sellar diaphragm, dried with filter paper and weighed with its capsule and a part of the stalk about 3—4 mm long. This procedure obviates mechanical injuries during preparation. The fixing medium was chosen because it is simple, is used as the standard method at this laboratory, and has proved suitable for all the organs and staining methods coming into question in this work.

On the other hand, the weighing of fixed organs involves the source of error provided by the fixing medium's influence. However, as the fixing time was, in the main, the same for all organs and cases, a systematic error can hardly have been introduced (see further below, concerning the adrenals).

After fixing, the hypophysis was divided with a razor blade by three sagittal cuts, one through the centre and one on each side of this through a point midway between the central

point and the lateral pole. The parts were embedded in paraffin, and 5 μ sections were made as near as possible to the cut surfaces. In some cases of the main material (cases from the beginning of the investigation) a 5 μ section horizontally through the central point of the anterior lobe has been used, instead. Only sagittal sections were used in the differential count, however. The sections were stained with haematoxylin-Magdala red (Grübler), since this staining method has proved suitable on account of a sharp red colouration of the acidophile granules, good nuclear staining and good colouration of the basophile granules, making it easy to identify the special cell forms observed earlier in the adrenogenital syndrome (hyaline basophiles and hypertrophic amphophiles; cf. Gellerstedt 1939, and Mellgren 1942). In this respect, stainings according to Crooke and Russel (1935), Wallart and Houette (1934), Wallraff (1939) and Romeis (resorcin-fuchsin method, 1940) have proved less appropriate in special tests. Haematoxylin-Magdala red has the further advantage that the results of the differential counts should, in the applicable parts, be directly comparable with those reported by Floderus (1944) after haematoxylin-eosin staining.

CLASSIFICATION OF THE PITUITARY CELLS

In the histological examination of the hypophysis sections the cells have been divided up into acidophiles, densely granulated (normal) basophiles, sparsely granulated basophiles, chromophobes with small nuclei (ordinary), chromophobes with large nuclei, and special cell forms (hyaline basophiles and hypertrophic amphophiles).

Acidophiles. These cells require no definition. They have been studied particularly in respect of the relative number, the presence of very small forms, and the size of the nucleus.

Basophiles. Basophiles have been taken to include all cells with distinct basophilic granules, *i. e.* β-cells. The boundary-line between densely granulated and sparsely granulated baso-

philes is admittedly vague, but as the investigations into the standard error of the method of the differential count show, it can be assessed with sufficient accuracy to be reliable from this technical viewpoint (see below). The sparsely granulated basophiles probably correspond to Romeis's (1940) hypochromatic β-cells, for in some cases neighbouring 5 μ sections have been stained, one after Romeis, the other with haematoxylin-Magdala red. When the two sections were compared, parts of the same cells could be identified in both, appearing as sparsely granulated basophiles in haematoxylin-Magdala red, and as hypochromatic β-cells according to Romeis's description in resorcin-fuchsin. Incidentally, this description is also very applicable to the sparsely granulated basophiles in haematoxylin-Magdala red: large as normal basophiles or somewhat larger, sparsely granulated, often with vacuoles, the nucleus small or — often — large, and poor in chromatin, seemingly hollow and sometimes with irregular outline. The coloured drawing (fig. 18) shows a typical cell of this kind. The sparsely granulated basophiles have been registered in this thesis because they form an intermediate link between normal basophiles and the hypertrophic amphophiles observed in the adrenogenital syndrome.

Special cells. This designation is used to cover the above-mentioned hypertrophic amphophiles and hyaline basophiles. *The hypertrophic amphophiles* are characterised by a large cellular body, often appreciably larger than that of the basophiles, and by foamy or finely granulated protoplasm, which responds to haematoxylin-Magdala red staining with a very faint violet colour. The cell contour is usually not clear cut. Most characteristic, however, is the large, seemingly distended nucleus with sparse, usually peripheral chromatin, sometimes irregular or polymorphous, and sometimes with a large or even gigantic acidophile nucleolus. The coloured drawing (fig. 18) shows several typical cells of this kind.

When making the differential count, it has been desirable to fix *one* criterion for demarcating the hypertrophic amphophiles from other chromophobe cells. For more than one

reason, the size of the nucleus has been chosen to this end. As was stated in the survey of the literature, the appreciable size of the nucleus in the hypertrophic amphophiles and in Crooke's cells is probably a morphological sign of increased cellular function. The size of the nucleus can therefore be regarded as an important characteristic. Furthermore, unlike the chromatin density and the size of the cellular body, the size of the nucleus is easy to measure objectively and with relative exactitude. Finally, it can be assumed *a priori* that the size of the nucleus is far less affected by decomposition in the cadaver and by the technical treatment of the specimens than are the cellular bodies: the protoplasm of the chromophobe cells is, in particular, sensitive to the sources of error mentioned (cf. Romeis 1940; and others).

In the differential count, then, hypertrophic amphophiles have been taken to include all chromophobe cells with a nucleus larger than 8.2×8.2 µ or 11×6 µ, when the greatest and smallest nuclear diameters were measured in the section (*i. e.* broadly speaking, larger than 50 μ^2 in the plane of the section. For the technique in measuring and differential count, see below). By this means, isolated cells have been registered as hypertrophic amphophiles in the cellular count, although they lacked one or more of this form's other characteristics, such as a large cellular body or a nucleus poor in chromatin. The atypical examples have nevertheless proved to be very few.

Basophiles with unquestionable, pale-pink hyaline fields in the cellular body have been registered as *hyaline basophiles* (Crooke's cells), whether or not they presented the other features, *i. e.* the large nucleus poor in chromatin, the sharp cell contour and the faintly tingible, powdery remains of basophile granules, which are typical of Crooke's cells on staining with haematoxylin-Magdala red or haematoxylin-eosin (cf. Gellerstedt 1939, and Mellgren 1942). As a rule, however, the hyaline cells have been typical Crooke's cells, specially in those cases where they occurred in abundance. The difficulty of distinguishing the hyaline basophiles from those in so-called colloid degeneration has seldom been encountered, since the colloid — as comparisons with sections stained according to

Kraus (1914) have shown — usually stains more deeply with haematoxylin-Magdala red than do the hyaline fields in Crooke's cells, and furthermore because the hyaline basophiles almost always showed *some* characteristic besides the hyaline structures, such as typical large nucleus or typical granular remains or typical shape in the hyaline fields (ring shape etc., cf. Gellerstedt 1939). In doubtful cases the cell was not accounted hyaline. The coloured drawing (fig. 18) illustrates some different types of hyaline basophiles.

Chromophobes. In the differential count these cells have been divided up into those with large nuclei and those with small (ordinary). There are several reasons for this. In the first place there seems to be a natural boundary between them, in that the ordinary chromophobes ('Hauptzellen') usually have a small dark nucleus and very sparse protoplasm, while the chromophobes with large nucleus as a rule have a larger cellular body, also, and are poor in chromatin (cf. Kraus 1926, and Romeis 1940). To this latter cell group plainly belong the 'transitional cells' and the 'degranulated chromophiles' which Kraus (1926) assumed to be granule-free chromophiles in their preliminary and final stages respectively; the same applies to the 'degranulated chromophiles' of Romeis (1940). Severinghaus (1937) also takes larger chromophobes to be granule-free functional stages of basophiles and eosinophiles, due to the observation that, in the rat, the Golgi apparatus in these chromophobes has the characteristic appearance of either the eosinophiles or the basophiles (Severinghaus 1933, 1937). It is true that Severinghaus's findings could not be confirmed by Farkas (1941) on man. Other authors (Comte 1898, and others, cf. survey in Floderus 1944) deny any genetic connection between the different cell types of the anterior pituitary lobe at all. All the same, it cannot definitely be said that a number of the large chromophobes are not normal functional stages of the basophiles, particularly since these latter and the chromophobes occur together (Floderus 1944). On the other hand, the hypertrophic amphophiles have been taken to be pathological functional stages of the basophiles

(see above). The boundary between these and the large chromophobes has been conditionally set in this investigation. It is therefore clear why the latter should also be registered.

For technical reasons, the dividing-line between the chromophobes with large and with small nuclei has been drawn at a nuclear diameter of 5.5 × 5.5 μ (roughly speaking, a nuclear surface of 25 μ^2 in the section's plane). As a number of cells are border-line cases, the division will be only approximate. (For the exactitude, see below.) Doubtful cases have been relegated to the small-celled group.

DIFFERENTIAL COUNT OF THE ANTERIOR PITUITARY

This, in common with all the other histological examinations, has been performed by the author himself. The method resembles that used by Floderus (1944). Thus, a binocular Zeiss microscope was used in the count. Ocular K 7 ×, objective 90 ×, immersion. In one ocular was placed an ocular net micrometer, consisting of a net 1 × 1 cm, and composed of 20 × 20 squares. In the optical system given, the side of 1 square corresponded to 5.495 μ in the object. 8.2 μ, *i. e.* the lower limit for the diameter of round nuclei in hypertrophic amphophiles, thus corresponded to 1.5 sides of a square, or rather over a square diagonal. In the same way, the lower limit of greatly excentric nuclei of hypertrophic amphophiles corresponded to rather over 1 × 2 sides of a square, and the boundary between chromophobes with large and with small nuclei was 1 side of a square.

The sections had been mounted on the slides so that the sagittal longitudinal axis of the hypophysis was parallel or nearly parallel with the long side of the slide. In the cell count, the slide was successively moved transversely to the longitudinal axis of the hypophysis. The successive shifting of the slide appears from fig. 1. The count began at the width of a squared net from the anterior pole. The stalk was marked off according to Floderus in the way shown in the figure. The 'intermediate lobe' was included with the exception of the regions between large colloid cysts and the posterior

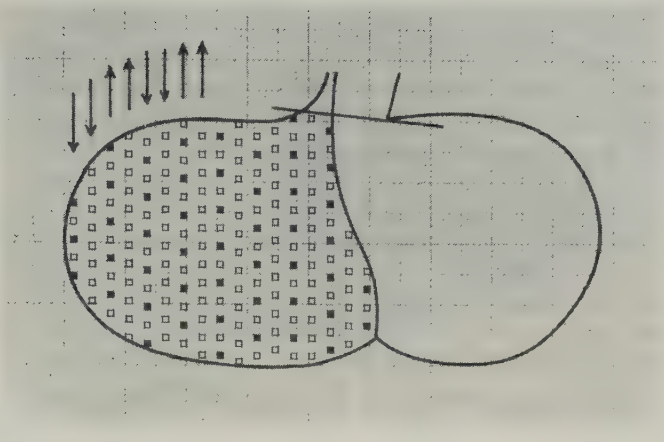

Fig. 1. Diagram of the differential count of the anterior pituitary, median section. The dark squares denote the areas within which cells of all the 7 described types were counted. The light squares denote areas within which only the special cells were counted. The arrows mark the successive moving of the visual field over the section.

lobe. The basophiles in the posterior lobe tissue were, on the other hand, not included in the count.

In this way the author counted nuclei of all special cells (hyaline basophiles and hypertrophic amphophiles) in every 3rd square of every 3rd row, and nuclei of other cells in every 6th square of every 6th row (see fig. 1). As the count always began with a square where all the cells (or, properly, nuclei) were counted, and as the nature of the row last counted is conditioned by chance, the proportion between completely reckoned squares and the total number of squares has varied from slide to slide, and seldom been precisely 1:4. The actual proportion was noted for each separate slide. The number of special cells (or, properly, the number of nuclei of such cells) was multiplied by this factor, after which the frequency of the different cell types was worked out in per cent. The aim of this procedure was to determine the frequency of the relatively few special cells with something approaching the same accuracy as in the other types. The calculation is based on the assumption that the cellular density is, on the average, the same in the completely counted squares on the one hand, and in the total number of counted squares on the other.

This assumption has proved justified (see below, on the method error).

The cell count described was performed on each of the 3 sagittal hypophysis sections of the cases given in table 1. Finally, the mean frequency of the different cell types, calculated on the total of each type, has been worked out in per cent for each case. Thus, regard has been paid to the different size (the different number of cells counted) of each section. In this way, 1,500—2,000 cells have usually been counted per section (including about 30 special cells; mean of the entire main material). The total number of counted cells per hypophysis usually amounted to rather over 5,000.

On the other hand, no reduction was made for the influence which the size of the nuclei has on the frequencies found. As was pointed out by Jonson (1908, 1909) and others, every count of the number of form elements within a certain surface of a histological section leads to too high values, since a number of bodies are divided by the histological sectioning, so that parts of the same body fall on two or more sections. An acceptable correction formula for this source of error has been worked out by Floderus (1944); it has been applied in the calculation of the total number of cells per volume unit of tissue, though never for correcting the frequency in the differential count. However, Floderus's investigation also shows how far large units (in this case, nuclei), are over-represented in the count in relation to small ones. When Floderus's formula is tested out on this material, then, it is found that the number of the largest nuclei (diameter about 10 μ) should be multiplied by about 0.70 if the number of the smallest (diameter about 5 μ) is multiplied by 1 before the frequencies are worked out. As the whole material contains many more cells with small nuclei than those with large, the lack of correction according to Floderus means that the frequencies of the cells with small nuclei are a few % too small, and the frequencies for the very largest (hypertrophic amphophiles) are some 20 or more % too large. No disadvantage is hereby involved, however, since the entire material has been investigated and calculated uniformly, and, in principle, in the same way

as that of earlier investigators. It should merely be remembered that the frequencies found are comparison values, 'automatically shifted' upwards when a certain cell type occurred with unusually large nuclei, and downwards, when the nuclei were small.

ESTIMATE OF THE CELL FREQUENCIES OF THE ANTERIOR PITUITARY LOBE

In those cases where the anterior pituitary lobe was investigated without a differential count (see table 1), Leitz's comparison microscope was used. The frequency of the described cell types was then estimated in comparison with specimens on which a differential count had been made, corresponding areas of the two specimens being successively focused. The hypophyses thus investigated without a cell count have greatly helped to expand the material over the special cell forms. In the comparison these forms were noted as definitely more than 0.55 % (which can be regarded as the upper limit for the normal; see below), as less than 0.55 %, or as 'doubtful'. For the exactitude of the method, see below.

Besides the cell count or the assessment of the cell frequency, the colloid in the anterior lobe and the 'intermediate lobe' has been approximately noted, as also the degree of 'basophile invasion' in the posterior lobe — both these factors according to the rough scale of 'slight', 'medium' or 'strong'. Finally, the posterior lobe has been investigated for the occurrence of perceptible pathological changes.

SOURCES OF ERROR WHEN DETERMINING THE FREQUENCY OF THE PITUITARY CELLS

When establishing the frequency values for the different cell types in any given case (mean of 3 sections), one plainly has to take into account six main sources of error — quite apart from the above-mentioned influence from the size of the nuclei. In the first place, the distribution of the different cell types in any one case may be atypical, so that the frequency figures will not be representative or fully comparable with those of another case. As Floderus showed (1944), however,

it should be possible to calculate on a fairly hard-and-fast cellular distribution. Secondly, decomposition or auto-digestion during the time between death and the fixing of the hypophysis may be expected to change the cellular picture. The magnitude of this source of error is unknown. Thirdly, errors may arise from cutting, so that the three sagittal sections do not lie in the intended plane. Needless to say, this source of error always plays some part, but its effect is not known. Fourthly, errors may arise from the histo-technique (different degrees of shrivelling, varying staining strengths, etc.) and fifthly, the cell count itself must make for errors when assessing the type cell for cell, particularly since the count is combined with measurement of the size of the nuclei.

There is no reason to assume that any of these errors are of a systematic kind, upsetting the comparison between different categories of cases. This might, however, be true of the — probably most important — psychological source of error, necessarily set up by the risk of assuming similar values in similar cases (*e. g.* the tendency to take more basophiles to be hyaline in cases of menopausal syndromes than in normal women). This error has been excluded as far as possible by making a differential count of most of the cases (59 of the 78 adults in the main material, and all 5 cases with diabetes) without knowing the diagnosis. The values in these 'blindly counted' cases do not differ systematically from the rest.

Of the other errors, the fifth (and, to a certain extent, the fourth) can be demonstrated by double determinations of separate sections. It has not been considered necessary thus to establish the standard error of the count for the individual section, but table 4 gives an idea of its size. The table shows double determinations performed in pairs on each of four different sections, each from one case. The cases and the sections have been chosen to include different kinds of case, and sections with different sizes and intensity of staining. The first count of each section was made according to the description, and the second backwards (beginning from the boundary of the posterior lobe). As appears, the errors in the actual count are generally very small.

Table 4. Double determinations in pairs on the same hypophysis section.

The individual sections on which the double determination was made		Correction factor = K = number of completely counted squares: whole number of squares	Cell types top figure = absolute number, lower figure = % 1. Acidophiles	2. Normal basophiles	3. Sparsely granulated basophiles	4. Total 2. + 3.	5. Chromophobes with small nuclei	6. Chromophobes with large nuclei	7. Total 5. + 6.	8. Hyaline basophiles	9. Hypertrophic amphophiles	10. Total 8. + 9.	11. Total 1. + 4. + 7.	12. Total 11. + K × Total 10.
O. $^{408}/_{42}$.	1st	16	474	75	40	115	509	114	623	2	16	18	1212	1217
25-year-old woman, normal, lateral section	count	61	38.9	6.2	3.3	9.4	41.8	9.4	51.2	0.04	0.34	0.39		100
	2nd	16	456	70	50	120	505	114	619	1	15	16	1195	1200
	count	56	38.0	5.8	4.2	10.0	42.1	9.5	51.6	0.02	0.36	0.38		100
O. $^{107}/_{44}$.	1st	11	142	112	56	168	292	36	328	0	7	7	638	640
67-year-old man, normal, median section	count	40	22.2	17.5	8.8	26.3	45.6	5.6	51.3	0	0.30	0.30		100
	2nd	11	152	102	72	174	300	26	326	0	6	6	652	654
	count	39	23.3	15.6	11.0	26.6	45.9	4.0	49.9	0	0.26	0.26		100
O. $^{477}/_{44}$.	1st	21	603	119	91	210	482	88	570	2	22	24	1383	1389
70-year-old man, prostatic hypertrophy, lateral section	count	79	43.4	8.6	6.5	15.1	34.7	6.3	41.0	0.04	0.42	0.46		100
	2nd	26	693	133	105	238	589	105	694	3	25	28	1625	1633
	count	87	42.4	8 1	6.4	14.6	36.0	6.4	42.5	0.05	0.46	0.51		100
O. $^{164}/_{43}$.	1st	63	1451	255	92	347	1676	468	2144	1	63	64	3942	3960
56-year-old woman, hyperparathyroidism, lateral section	count	222	36.6	6.4	2.3	8.8	42.3	11.8	54.1	0.01	0.45	0.46		100
	2nd	56	1162	243	101	344	1599	400	1999	2	60	62	3505	3522
	count	201	33.0	6.9	2.9	9.8	45.4	11.4	56.8	0.02	0.47	0.49		100

However, far greater interest attaches to the collected effect of atypical cell distribution, errors in cutting, errors from the histo-technique, and errors arising at the actual count. For it may well be this collected effect that mainly determines the standard error of the mean value of the frequency in a given cell type in any one case, *i. e.* the standard error of the mean calculated on the three sagittal sections.[1]

This standard error can be determined on the difference between the lateral sections for each case. That is to say, it is obvious that if all the errors mentioned were 0, the frequency value of a given cell type in a lateral section would be identical with the corresponding value in the other lateral section of the same case.

Table 5 gives the results of a determination of this kind for the frequency of three cell types, namely the special cells, basophiles poor in granules, and chromophobes. These three types have been chosen because it could be assumed that the two first would give the least exact values, and the last-mentioned type the most exact values. The calculation has been made on the 87 first counted cases of the main material, diabetics and cases with hyperparathyroidism. It may be added that in the remaining cases where a differential count was made, the differences have been smaller rather than anything else. σ_i in the tables has been calculated on the differences between the two lateral sections, and denotes the standard error of a single determination (on one lateral section). $\varepsilon(M_i)$ denotes the standard error of the mean for one case (M_i for 2 lateral sections and one median section) and has been calculated on the reasonable assumption that σ_i for a median section is as large as σ_i for a lateral section.

[1] This thesis employs current formulas according to G. Dahlberg: 'Statistical Methods for Medical and Biological Students', London 1940.

A rule followed throughout is, that when groups comprising at least 15 individuals each have been compared, 3 times the standard error of the difference has been taken to indicate a significant difference, and 2 1/2 times the standard error a probable difference. It might, however, be mentioned that R. A. Fisher and co-workers usually calculate that a difference is significant with twice the standard error.

Table 5. Standard error of a single determination (σ_i) and of mean for one case [$\varepsilon(M_i)$].

Calculated on the difference between the separate lateral sections (d) for each case.

Cell types	Number of investigated cases N	Mean of all cases M	Stand. error of single determination $\sigma_i = \pm\sqrt{\frac{\Sigma d^2}{2N}}$	Stand. error of single case $\varepsilon(M_i) = \pm\frac{\sigma i}{\sqrt{3}}$	Stand. error of single case in % of M $= \pm\frac{\varepsilon(M_i)}{M}\cdot 100$
1. Special cell types Absolute values . . .	87	88	13.33	7.696	8.7
2. Special cell types Frequency (%) . . .	87	0.47	0.13	0.075	16
3. Sparsely granulated basophiles Frequency (%)	87	5.8	1.71	0.988	17
4. Chromophobes (small and large nuclei) . . Frequency (%) . . .	87	55	5.58	3.221	5.9

As appears, the values for the dispersion are far less when the calculation is based on the absolute figures than when the frequency figures are used (cf. lines 1 and 2 in table 5). This is obviously because the different sizes of the sections influence the relative and the absolute values to different extents. That is to say, the absolute value for d may be small between the smallest sections, regardless of whether the relative value for d is large or small, while the converse risk should not appear with the same force when large sections are compared. It should therefore be most correct to rely on the values for the standard error, which have been based on the frequency figures of d (lines 2, 3 and 4 in table 5). The values in table 5 show a fully adequate exactitude of method when compared with the variations observed from case to case.

The source of error which decomposition may constitute, finally, has been investigated by determining the correlation between the time from death to autopsy, and the frequency of special cell types in the anterior pituitary lobe of the 76 first cases with differential count (embracing endocrinely normal, menopausal syndromes, prostatic hypertrophy and cases of diabetes). There was no correlation, for the correlation coef-

ficient (according to Bravais-Pearson) was found to be -0.084 ± 0.114. Table 6 shows the same situation in another form.

Table 6. Correlation between the frequency of the special cell types in the anterior pituitary and the interval between death and autopsy.

Frequency of the special cell types in % . . .	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
Number of cases with frequency in question	3	12	14	7	17	8	6	4	2	3
Interval death–autopsy in cases in question (mean)	30.0	16.4	22.1	18.3	24.4	14.5	16.3	18.0	9.5	20.3

Nor did the separate groups within the main material show any correlation between the frequency of the special cell types and the time from death to autopsy. The normal old women (differential count in 15 cases, on an average low frequency values for the special cells) showed an average time of 12.8 hours between death and autopsy, the cases with menopausal syndromes (18 cases, high frequency values) had a mean of 17.3 hours, but normal old men (12 cases, low frequency values) had a mean of 31.2 hours, and cases of prostatic hypertrophy (12 cases, high frequency values) had, conversely, a relatively short time between death and autopsy, namely 15.3 hours. Thus, this source of error cannot be very important.

Table 7. Comparison between the differential count and estimate of the frequency of the special cells in the anterior pituitary lobe.

Row 1 gives the Case No. (1944). — Row 2 gives the result of the diff. count in %. — Row 3 gives the same frequency estimated with the comparison microscope, — indicating < 0.55 %, and + indicating > 0.55 %.

1.	55	6	91	36	74	27	44	11	77	70
2.	0.11	0.17	0.17	0.29	0.31	0.36	0.37	0.39	0.42	0.43
3.	—	—	—	—	—	—	—	—	?	—
1.	47	86	25	71	41	14	37	20	12	21
2.	0.44	0.45	0.56	0.61	0.61	0.64	0.69	0.80	1.04	1.22
3.	?	—	? or ±	+	+	? or −	? or +	+	+	?

The reliability of the estimated cell frequency, when the anterior pituitary lobe was investigated without a differential count, is illustrated by table 7. This table gives the results of a comparison between estimate and differential count, as regards the special cell types. The comparison was performed on the median section of the 20 cases with the lowest registration number, on whom the differential count was made in 1944. The assessment was made in ignorance of the results of the count. The results show fairly good agreement between the methods.

The Adrenals

These organs were removed with surrounding fatty tissue, fixed in 10 % formalin for about 10 days (not less than 5; only in single cases between 20 and 30 days), carefully freed from the surrounding fat, and weighed.

Weight. The adrenals are the only endocrine organs which showed any major differences in weight between the different groups of cases in this investigation. It has therefore been considered necessary to investigate the influence of fixing on the weight of the adrenals. 20 adrenals from 10 consecutive adult autopsy cases were thus freed from surrounding fatty tissue, weighed in a fresh condition and subsequently at different intervals after fixing in 10 % formalin; see table 8. The results admittedly seem to indicate that the weight rises somewhat with a long fixing. However, the differences are so small that they cannot be established statistically in this material; in any case, they can hardly have any effect beside the great variations in the initial weight from case to case, as the technique used rules out any systematic difference of more than a week in the fixing time between different types of case.

Histological examination. After fixing, a slice from each adrenal was cut out at right angles to the longitudinal axis of the organ near the central point and embedded in paraffin. 5 μ sections from each were stained with Ponceau-Fuchsin

Table 8. Dependence of adrenal weight on fixing.

Autopsy No.	Adrenal weight in gm before fixing	Adrenal weight in % of initial weight										
		Before fixing	After fixing in 10 % fo., number of days									
			1.	2.	3.	4.	5.	6.	7.	14.	21.	28.–30.
475/44	5.75	100	103	102	—	99	100	101	99	106	106	106
	7.40	100	101	99	—	100	97	96	101	105	105	105
476/44	5.05	100	105	100	—	99	99	99	100	102	107	107
	5.40	100	99	100	—	96	94	94	104	104	106	104
477/44	6.05	100	101	98	—	98	93	93	96	101	101	101
	8.05	100	103	100	—	97	89	94	96	99	103	102
479/44	7.70	100	—	94	92	91	96	99	97	99	99	100
	5.60	100	—	98	91	92	98	100	98	100	100	102
481/44	8.30	100	101	101	101	—	105	104	102	102	102	102
	7.60	100	100	101	101	—	104	101	101	104	105	105
483/44	5.30	100	108	108	—	109	108	106	106	109	109	109
	6.50	100	102	98	—	102	100	98	100	102	102	102
486/44	3.00	100	103	97	103	100	100	—	100	107	107	110
	4.50	100	102	98	98	98	100	—	98	102	102	104
487/44	3.70	100	100	97	97	100	103	—	100	97	97	105
	2.70	100	104	104	100	107	107	—	104	107	111	115
488/44	4.90	100	100	102	102	102	—	102	102	100	100	100
	5.30	100	100	100	98	100	—	100	100	100	102	100
490/44	4.20	100	105	—	105	105	107	102	102	102	105	105
	3.50	100	106	—	103	103	106	106	111	109	109	111
Mean weight		100	102.3	99.8	99.2	99.8	100.3	99.6	100.8	102.8	103.9	104.7

according to Vines (Broster, Allen, Vines *et al.* 1938). In addition, a frozen fat-stained section, about 15 μ thick, from the one adrenal was investigated for content and distribution of lipoid.

When investigating the embedded sections under the microscope, regard was paid to two factors in particular, namely the width of the cortex, and the PFR. The former was assessed with small magnification, after which 5 such cortical portions which appeared representative of the section were measured, and the medium of the measurements given. The results of the PFR were assessed on the scale 'negative', 'uncertain', 'positive' and 'strongly positive'. A negative reaction was one where no sharply red-stained granules occurred in the cortical cells, a positive (or, more correctly, weakly positive) reaction was one where sharply red-granulated cells occurred in single groups or in an abundance of separate examples.

The coloured photographs, figs. 19—22, show examples of positive reaction. The PFR was considered strongly positive when there was very copious acidophile granulation. When the reaction was definitely positive in the cortex of one adrenal, but doubtful or negative in the other, the case was reckoned positive. It must be admitted that the limits in this scale are not clear cut. Table 9 outlines the degree of consistency with which they could be maintained. The table covers the results of double determinations of the PFR on 40 adrenals from 20 cases, arbitrarily chosen by an assistant, and investigated (2nd determination) in ignorance of the result of the 1st determination, which had been made more than two months previously.

Table 9. Double determination of PFR in the adrenal cortex.

Strongly positive reaction: + + Doubtful: ?

	No. of case	25/44	20/44	87/44	408/43	140/43	74/44	54/43	399/43	86/44	127/44	81/44	112/44	47/44	108/43	107/41	93/44	192/44	149/44	157/44	198/41
PFR	at control examination	1st adrenal	—	+	—	+ +	+	?	—	—	—	+	+	+	+	+	—	–	?	—	+	—	—	—
		2nd adrenal	—	?	—	+ +	+	–	–	—	?	+	—	+	+	?	—	?	—	+	–	–		
	at 1st examination	1st adrenal	—	+	—	+ +	+	—	+	?	+	+	+	+	+	+	—	+	—	+	—	—	—
		2nd adrenal	–	+	–	+ +	+	—	+	?	+	—	+	+	+	—	+	—	+				

In 2 of the 20 cases there was a clear discrepancy between the results, and in a further 3 there was some difference. As regards the actual assessment, then, the method can be considered fairly reliable, when large groups of cases are to be compared. This should also apply when other sources of error have been taken into account. That is to say, no systematic difference between the different groups of cases could be traced concerning the histo-technique, and cadaver changes do not have much effect: on the first 100 cases investigated, the time from death to autopsy was found, on an average, to be the same with positive and with negative PFR. When the material was divided to give the numerically largest correlation coefficient between positive PFR and a long interval between

death and autopsy, we get $r = -0.067 \pm 0.100$ (Bernoullian coefficient; cf. table 10).

Table 10. Interval between death and autopsy in hours (1) and PFR (2).

Doubtful and border-line cases have been divided (half the cases to each column).

1. / 2.	> 30	< 30	Total
PFR+	5.0	30.5	35.5
PFR−	12.5	52.0	64.5
Total	17.5	82.5	100.0

As regards the separate groups in the main material, there is the same lack of correlation between the time from death to autopsy and the result of the PFR, as between the former factor and the frequency of special cells in the anterior pituitary lobe.

Other Endocrine Organs

These were fixed in 10 % formalin, weighed, and investigated histologically, usually on 10 μ paraffin sections.

The epiphysis was cut sagittally near the middle. The sections were stained according to van Gieson. The investigation gave special attention to 'Kerneinschlüsse', since they were considered to have a connection with the secretion of the organ (Berblinger 1926).

The thyroid sections were stained according both to van Gieson and to Kraus's colloid staining (Kraus 1914).

The parathyroids were usually examined macroscopically only. When they were sectioned, eosin-stained paraffin sections and fat-stained gelatin sections were used.

The cauda pancreatis was examined histologically on van Gieson stained paraffin sections and frozen sections stained with gentian violet, the latter on account of Gellerstedt's (1938 b) observation of the correlation between amyloidosis in the islets and diabetes. Attempts to use silver staining according to Ferner (1942, Gross-Schultze's method) and azan staining to assess

the proportions of A- and B-cells in the islets yielded too uncertain results, obviously due to the fact that the material was not, as a rule, sufficiently fresh.

The ovaries and testes were investigated on paraffin sections stained according to van Gieson.

The endometrium in the body of the uterus was examined histologically in several of the older women with menopausal syndromes on paraffin sections stained according to van Gieson. The same method of examination was also used on all the fertile women; with few exceptions, staining according to Hølund (1944) was also made on these latter sections, to show the mucine and establish the phase of the uterus mucosa in the menstrual cycle.

CHAPTER V

RESULTS

1. NORMAL ADULTS

THE HYPOPHYSIS

WEIGHT. The weight of the hypophysis of men and women at different ages appears from table 11. The weights are as a rule somewhat higher than those which Berblinger (1932) and others found on large materials; this may possibly be because, in this investigations, the organs had been fixed.

Table 11. The weight of the fixed hypophysis in normal men and women.

Men			Women		
Age in years	Number of cases	Weight in mg mean with standard error	Age in years	Number of cases	Weight in mg mean with standard error
16—19	1	712	16—19	2	897
20—29	2	701	20—29	3	692
30—39	1	837	30—39	4	701
40—49	10	824	40—49	2	967
50—59	12	707	50—59	7	789
60—69	15	762	60—69	9	831
70—79	7	753	70—79	7	852
80—89	1	757	80—89	4	786
90—99	0	—	90—99	1	828
18—48 mean 38.8	14	800 (± 32)	16—46 mean 28.5[1]	10	755
50—81 mean 63.1	35	741 ± 20	49—99 mean 67.9[2]	29	827 ± 22
66—81 mean 70.5	16	769 ± 28			
18—81	49	758 ± 17	16—99	39	809 ± 21

[1] Before menopause.

[2] In menopause.

The only other noteworthy point emerging from a comparison with the results of earlier investigators is the high weight in young men (cf. Rasmussen 1928, 1934; Berblinger 1932; and Floderus 1944). The compilation in table 11 is mainly intended for comparison with the pathological cases (see below).

Table 12. Frequency of different cell types in the anterior pituitary of endocrinely normal men.

The mean of the 3 sagittal sections in % has been given for each case and cell type.

Case No.	Age in years	Frequency of different cell types in %									
		1. Acidophiles	2. Normal basophiles	3. Sparsely granulated basoph.	4. Total 2. + 3.	5. Chromophobes with small nuclei	6. Chromophobes with large nuclei	7. Total 5. + 6.	8. Hyaline basophiles	9. Hypertrophic amphophiles	10. Total 8. + 9.
$^{93}/_{44}$	18	40	6.5	3.8	10	44	5.8	50	0.01	0.41	0.42
$^{460}/_{42}$	21	33	6.3	5.6	12	48	7.3	55	0.00	0.36	0.36
$^{41}/_{44}$	35	23	8.1	4.3	12	54	10.	64	0.00	0.51	0.51
$^{71}/_{44}$ [1]	44	34	7.6	5.9	13	45	6.7	52	0.04	0.67	0.71
$^{74}/_{44}$	44	38	6.1	4.5	11	47	3.9	51	0.01	0.26	0.26
$^{86}/_{44}$ [2]	45	31	11.	3.6	14	50	4.5	54	0.00	0.38	0.38
$^{397}/_{42}$	46	28	12.	7.7	19	47	4.9	52	0.07	0.43	0.50
7 cases 18–46 yrs Mean 36.1 yrs		32.4	8.2	5.1	13.0	47.9	6.2	54.0	0.02	0.43	0.45
$^{454}/_{42}$	50	35	6.8	5.9	13	45	6.8	52	0.03	0.42	0.45
$^{150}/_{44}$	51	43	6.0	3.8	10	43	3.9	47	0.01	0.19	0.20
$^{462}/_{42}$	58	26	25.	5.7	30	41	2.3	43	0.32	0.16	0.48
$^{6}/_{44}$	63	34	9.4	1.1	10	50	5.9	55	0.04	0.28	0.32
$^{70}/_{44}$ [3]	66	37	12.	6.8	18	38	6.2	44	0.03	0.44	0.46
$^{77}/_{44}$	66	35	12.	3.1	15	44	6.0	50	0.03	0.44	0.47
$^{11}/_{44}$	66	31	8.1	2.5	11	53	4.9	58	0.03	0.35	0.38
$^{107}/_{44}$	67	32	12.	6.5	19	44	4.4	48	0.00	0.25	0.25
$^{127}/_{44}$	67	28	11.	7.2	18	47	5.8	53	0.05	0.27	0.32
$^{55}/_{44}$	67	26	6.5	5.8	12	55	6.8	62	0.00	0.17	0.17
$^{27}/_{44}$ [4]	68	20	25.	2.6	28	48	3.4	52	0.05	0.29	0.35
$^{112}/_{44}$ [5]	81	38	12.	3.3	15	45	5.9	51	0.05	0.29	0.34
12 cases 50–81 yrs Mean 64.2 yrs		31.7	12.2	4.5	16.6	46.1	5.2	51.3	0.05	0.30	0.35

[1] Meningitis purulenta.

[2] Mixed basophile-chromophobe adenoma.

[3] Chromophobe adenoma.

[4] Basophile adenoma.

[5] 2 chromophobe adenomas.

Table 13. Frequency of different cell types in the anterior pituitary of endocrinely normal women.

The mean of the 3 sagittal sections in % has been given for each case and cell type.

Case No.	Age in years	Frequency of the different cell types in %									
		1. Acidophiles	2. Normal basophiles	3. Sparsely granulated basophiles	4. Total 2. + 3.	5. Chromophobes with small nuclei	6. Chromophobes with large nuclei	7. Total 5. + 6.	8. Hyaline basophiles	9. Hypertrophic amphophiles	10. Total 8. + 9.
168/44	17	37	7.8	3.2	11.	46	5.7	52	0.02	0.32	0.34
37/44 [1]	18	43	5.0	7.4	12.	35	9.1	44	0.05	0.43	0.47
343/44 [1]	20	44	9.4	5.3	15.	36	5.0	41	0.03	0.24	0.28
Sö. 43	22	50	6.6	4.5	11.	32	6.2	38	0.03	0.28	0.31
337/43	23	29	2.7	4.6	7.3	44	19.	63	0.02	0.41	0.43
408/42	25	29	7.9	4.6	13.	49	9.1	58	0.02	0.27	0.29
26/43	25	47	5.7	4.0	9.7	37	6.1	43	0.00	0.12	0.12
333/43	26	45	4.1	4.3	8.4	38	8.0	46	0.04	0.21	0.25
333/42	27	31	13.	4.8	17.	39	12.	51	0.01	0.46	0.47
139/43	27	39	4.0	4.5	8.6	49	3.3	52	0.00	0.12	0.12
467/43	32	29	7.3	5.2	13.	53	5.7	58	0.00	0.22	0.22
19/43	34	24	7.1	6.3	13.	52	10.	62	0.02	0.22	0.24
160/44	38	43	6.2	3.5	9.6	40	6.6	47	0.03	0.49	0.52
149/44	46	28	8.1	6.3	14.	48	9.8	58	0.07	0.43	0.50
14 cases 17–46 yrs Mean 27.1 yrs		37.0	6.7	4.9	11.6	42.7	8.3	50.9	0.02	0.30	0.33
253/43	41	37	3.9	7.5	11.	36	16.	51	0.02	0.52	0.54
214/43	43	33	8.5	7.7	16.	43	6.9	50	0.03	0.16	0.18
328/43	51	27	6.8	7.7	14.	47	11.	58	0.01	0.54	0.55
147/43	57	30	5.6	3.6	9.2	50	10.	60	0.01	0.37	0.38
416/42	59	30	7.8	7.8	16.	47	7.3	54	0.05	0.16	0.21
47/44	60	28	9.0	4.5	14.	54	4.5	59	0.17	0.28	0.45
459/42	64	21	7.2	9.5	17.	49	13.	62	0.10	0.41	0.51
44/44	64	32	7.6	9.4	17.	41	8.9	50	0.01	0.33	0.34
414/43	73	32	6.7	3.6	10.	46	12.	58	0.03	0.31	0.34
309/42	77	39	6.5	5.0	12.	39	10.	49	0.03	0.47	0.50
334/43	77	31	7.9	5.8	14.	48	6.9	55	0.06	0.17	0.23
468/43	77	36	9.5	3.7	13.	47	3.8	51	0.07	0.09	0.16
458/42	81	26	8.2	3.2	11.	54	8.9	63	0.01	0.35	0.36
58/43	98	40	18.	4.0	22.	36	2.0	38	0.01	0.11	0.12
91/44	99	24	13.	2.5	16.	56	3.6	60	0.04	0.16	0.21
15 cases 41–99 yrs Mean 68.1 yrs		31.1	8.4	5.7	14.1	46.2	8.3	54.5	0.04	0.30	0.34

[1] Meningitis tb.

Histological structure. The results of the differential count of the anterior pituitary lobes appear from tables 12, 13 and 14.

Concerning the frequency of acidophiles, basophiles (total) and chromophobes (total), the results agree well with those which Rasmussen (1929, 1933) reported from a material of 100 men and 94 women, whose hypophyses had been cut horizontally, stained according to a modified Mallory technique, and differentially counted (3 sections per hypophysis) with a technique resembling the one used here, but with the cells divided up only into the three mentioned types. However, in tables 12—14, the values for acidophiles are throughout some % lower, and those for basophiles (total) some % higher, than those given by Rasmussen. The differences are statistically significant only for the acidophiles in fertile women, and for the basophiles in young and old women. The same differences, though somewhat more marked, come out when tables 12—14 are compared with the results of Floderus (1944); these are based on 40 men and 5 women, whose hypophyses were investigated with staining and a cell count with a technique very like that of the present author, but with a division into only three cell types. The differences cannot be explained by the present material's division into normal cases on one hand, and cases of menopausal syndromes and prostatic hypertrophy on the other (cf. below, and also Rasmussen 1929, 1933, and Floderus 1944). On the other hand, they might be due to the way in which the individual investigator has conceived of the different cell types.

The dispersion of the frequency value ($\sigma = \varepsilon(M) \cdot \sqrt{n}$) for each cell type and category of cases (table 14) is about as large, or somewhat smaller, than in Rasmussen (1929, 1933) and Floderus (1944).

In conformity with the results of the above-mentioned investigators, tables 12—14 show only quite small (not significant) differences between men and women, and for different ages. It should be specially noted that the higher frequency of special cells manifest in young men (table 14, column 10) is due to a single case with a very high frequency of this

Table 14. Frequency of different cell types in the anterior

Nature of cases	Number of cases	Frequency of the different			
		1. Acidophiles	2. Normal basophiles	3. Sparsely granulated basophiles	4. Total 2. + 3.
Men 18—46 yrs mean 36.1 yrs	7	32.4(± 2.19)	8.2(± 0.89)	5.1(± 0.55)	13.0(± 1.11)
Men 50—81 yrs mean 64.2 yrs	12	31.7 ± 1.74	12.2 ± 1.86	4.5 ± 0.58	16.6 ± 1.90
Women before menopause 17—46 yrs mean 27.1 yrs	14	37.0 ± 2.27	6.7 ± 0.66	4.9 ± 0.31	11.6 ± 0.75
Women in menopause 41—99 yrs mean 68.1 yrs	15	31.1 ± 1.40	8.4 ± 0.86	5.7 ± 0.61	14.1 ± 0.85

kind (table 12, case 71/44, 0.71 %). In this case there was purulent meningitis with infiltration in the pituitary capsule. It may be, therefore, that the value is misleading. As no other case among the normal subjects showed a greater frequency than 0.55 %, this latter figure has been taken as the 'practical' upper limit for the normal value of special cell types.

The differentially counted normal material is small. To increase it, the frequency of special cells has been estimated, without a count (see above), on a further 23 cases. Table 15 shows the results from the entire material.

Incidentally, it is conceivable that the frequency values of the special cells in the differentially counted material (tables 12—14) cannot, strictly speaking, be directly compared with the estimated values. In the former investigation the frequency values were consistently established as the means of 3 sagittal sections, but in the estimated material only one sagittal median section was used in certain cases, and in certain others only one horizontal section. However, a comparison of table 16 with table 14 shows the special cells to reveal very small differences between the frequency values established on 3 sagittal sections and those established in the same material on only 1 sagittal median section. Furthermore, a comparison with the works of Rasmussen (1929, 1933) and Floderus (1944) shows

pituitary. Endocrinely normal men and women together.

cell types in % $M \pm \varepsilon(M)$

5. Chromophobes with small nuclei	6. Chromophobes with large nuclei	7. Total 5. + 6.	8. Hyaline basophiles	9. Hypertrophic amphophiles	10. Total 8. + 9. = Special cell types
47.9(± 1.26)	6.2(± 0.79)	54.0(± 1.79)	0.019(± 0.010)	0.430(± 0.049)	0.449(± 0.054)
46.1 ± 1.40	5.2 ± 0.41	51.3 ± 1.58	0.053 ± 0.025	0.296 ± 0.029	0.349 ± 0.030
42.7 ± 1.83	8.3 ± 1.04	50.9 ± 2.14	0.024 ± 0.005	0.301 ± 0.033	0.326 ± 0.036
46.2 ± 1.61	8.3 ± 1.00	54.5 ± 1.69	0.043 ± 0.011	0.295 ± 0.038	0.339 ± 0.038

the difference between the frequencies of the three main cell types in horizontally and sagittally cut hypophyses respectively to be slight. There is therefore reason to assume that the special cells, too, are sufficiently evenly distributed to allow of direct comparisons between the frequency values from horizontal sections and those from sagittal sections.

Thus, it is clear that *the special cell types, i. e. hyaline basophiles and hypertrophic amphophiles, are normal elements in the*

Table 15. Occurrence of the special cells in the anterior pituitary.

Combined normal material of hypophyses differentially counted and examined under the comparison microscope.

Nature of cases	Total number of examined cases	Frequency of the special cells		
		Number of cases with > 0.55 %	Number of doubtful cases	Number of cases with ≦ 0.55 %
Men 18—48 years	11	1	0	10
Men 50—84 years	16	1	0	15
Women before menopause 16—46 years	21	0	2	19
Women in menopause 41—99 years	24	1	2	21[1]
Men + Women 16—99 years .	72	3	4	65

[1] 3 cases under 50 years, *i. e.* 41, 43 and 49 years old.

Table 16. Frequency of different cell types in the anterior in each

Nature of cases	Age in years, mean	Number of cases	Frequency of the different cell types			
			1. Acidophiles	2. Normal basophiles	3. Sparsely granulated basophiles	4. Total 2. + 3.
Normal men 18—81 years	53.8	19	23.3 ± 1.86 8.11	12.6 ± 1.84 8.00	5.4 ± 0.49 2.11	18.1 ± 1.85 8.06
Normal women 17—99 years	48.3	29	26.7 ± 2.23 12.0	9.2 ± 0.81 4.38	6.6 ± 0.46 2.46	15.8 ± 0.92 4.94

anterior pituitary, even though they seldom (3 cases in 72) occur to more than 0.55 %. They plainly occur in about the same frequency in endocrinely normal men and women, independent of age.

It has been stated earlier on that the occurrence of transitional forms between the hypertrophic amphophiles and the basophiles (and hyaline basophiles) has caused the former to be regarded as functional stages of the latter, and probably final stages of the hyaline change (cf. review of the literature above). In the present normal material also, the occurrence of such transitional forms between hyaline basophiles and hypertrophic amphophiles could be confirmed in all cases where hyaline basophiles were present; transitional forms between sparsely granulated basophiles and hypertrophic amphophiles occurred with absolute regularity. However, the question of the morphological genesis of the hypertrophic amphophiles seems particularly to involve the distribution of these cells within the individual hypophyses. Thus, in 45 of the 48 differentially counted normal hypophyses, the hypertrophic amphophiles appeared almost selectively among the basophile cells, and as a rule, though less pronounced, among the chromophobes, for as Floderus has shown earlier on (1944), basophiles and chromophobes usually occur more or less intimately mixed. Only in a 21-year-old man (O. 460/42) were numerous hypertrophic amphophiles found among the acidophiles also. Moreover, the hypertrophic amphophiles have a plain predi-

pituitary, established on one sagittal median section only separate case.

in % $M \pm \varepsilon(M)$; the lower figure gives σ

5. Chromophobes with small nuclei	6. Chromophobes with large nuclei	7. Total 5. + 6.	8. Hyaline basophiles	9. Hypertrophic amphophiles	10. Total 8. + 9.
52.2 ± 1.59 6.93	6.1 ± 0.57 2.47	58.3 ± 1.83 7.98	0.039 ± 0.015 0.067	0.35 ± 0.036 0.16	0.39 ± 0.033 0.14
48.3 ± 1.87 10.0	8.8 ± 0.83 4.48	57.2 ± 1.99 10.7	0.038 ± 0.010 0.052	0.30 ± 0.029 0.15	0.34 ± 0.030 0.16

lection for the hyaline basophiles in those cases where the latter cells occur in some abundance. It is therefore very likely that, *even in normal conditions, the hypertrophic amphophiles are developed from the basophiles (possibly via the hyaline change)*, at any rate for the most part. There is therefore good reason for dealing with them in connection with the hyaline basophiles, and this practice has been followed throughout in this thesis.

It has be found that, of the cell types investigated, the special cells (*i. e.* the hypertrophic amphophiles and the hyaline basophiles) are those which show the greatest frequency difference between the normal cases on the one hand, and cases with menopausal syndromes and prostatic hypertrophy on the other (see below). Even the normal material has therefore been investigated to see whether the special cells in question were correlated with obesity or cardiac hypertrophy (taken as an indication of hypertonia). This was not the case. 37 normal men and women with normal or reduced flesh had an average special-cell frequency of 0.36 %, and 11 fat normal cases had a frequency of 0.34 %. The 20 normal men and women with ordinary cardiac weight (for the men set at $\leqq$ 350 gm, and for the women $\leqq$ 300 gm) had a frequency of 0.34 %, and the 24 cases with cardiac hypertrophy had one of 0.38 % (in 4 cases there were no data as to the weight of the heart). Even without a calculation of the standard error, there is obviously no difference between the different groups.

Besides the differential count, it has been found that the acidophile cells have large nuclei poor in chromatin in about every 5th case, and with about the same frequency in men and women of different ages, and in 4 cases (2 women of fertile age, and 2 old men) of the 48 there were numerous acidophiles with very small cellular bodies. Table 17 shows the amount of colloid and the degree of 'basophile invasion' in the neurohypophysis. As secondary finding we would finally mention the occurrence of hyaline basophiles among the normal basophiles invading the posterior lobe of a 58-year-old man (O. 452/42). These findings will be touched on in connection with the pathological groups.

Table 17. Basophile invasion and colloid content in the normal material.

Nature of cases	Total number of examined cases	Basoph. invasion of neurohypophysis			Colloid content		
		slight	moderate	strong	slight	moderate	strong
Men 18—48 years . .	8	5	1	2	3	4	1
Men 50—84 years . .	14	6	3	5	5	7	2
Women before menopause 16—46 years	18	17	1	0	11	6	1
Women in menopause 41—99 years	19	11	1	7	6	11	2

THE ANTERIOR PITUITARY AND THE MENSTRUAL CYCLE

A correlation between the frequency of the special cells in the anterior pituitary and the phase of the menstrual cycle has been observed in women before the menopause; see table 18. The table has been drawn up on the following principles. First, the mean length in days of the normal menstrual cycle (m), and the time in days (t) elapsing between the beginning of the last menses and death have been noted for the individual case, on the case history. To be able to compare cases showing a habitually long cycle with cases showing a short one, the time t was then reduced according to the formula $T = \frac{m}{28} \cdot t$, where T is the day in a 28-day cycle when the case

Table 18. The menstrual cycle and frequency of the special cells in the anterior pituitary.

Cf. the text. In Cases 4—14 the histological pictures of the ovaries and of the uterus mucosa were normal, and agreed with one another in respect of the cycle's phase.

Case No.	*T* according to anamnesis	*H* Phase of the uterus mucosa histologically	*M* Day in cycle. Mean of anamnesis and histol.	Frequency of special cells in ant. pit.	Remarks
1 333/43	?	Early proliferation or atrophy	Inactive	0.25	Probably amenorrhœa for several months
2 408/42	20	Early proliferation	»	0.29	Discrepancy between *T* and *H*
3 168/44	27	» »	»	0.34	Discrepancy between *T* and *H*
4 19/43	?	» »	7	0.24	Normal cycle
5 139/43	?	» »	7	0.12	Probably normal cycle
6 26/43	?	» »	7	0.12	» » »
7 467/43	11	Late »	11	0.22	Normal cycle (?)
8 87/44	11	» »	11	0.47	» »
9 343/44	12	Unknown	12	0.28	» »
10 Sö. 43	12	Transf. prolif.-secret.	14	0.31	» » (?)
11 337/43	22	» » »	19	0.43	» »
12 333/42	19	Secretion	19	0.47	» »
13 149/44	18	»	18	0.50	» »
14 160/44	25	Late secretion	25	0.52	» »

was investigated. After this, the phase of the uterine mucosa was assessed histologically (for technique, see above). Finally, the day of the cycle (*M*) has been given as the mean of *T* and the mucosal phase in the 7 cases (Nos. 7, 8, 10, 11, 12, 13 and 14 in table 18) showing agreement or near agreement between these two criteria. In the 4 cases (Nos. 4, 5, 6 and 9 in the table 18) where only one of these two was known, *M* has been set according to it.

Leaving out of account Cases 1, 2 and 3 in table 18, where the cycle was not normal, a clear correlation is found between the day in the cycle and the frequency of the special cells in the anterior pituitary. The correlation coefficient (calculated according to Bravais-Pearson on the 11 cases Nos. 4—14) is $+0.77 \pm 0.12$. Of course, the material is just about as small as it could be to allow of a calculation of this kind. How-

ever, as the correlation coefficient has been found to be 5 times greater than its standard error, the positive correlation can be considered significant. Thus, *the frequency of hypertrophic amphophiles and hyaline basophiles in the anterior pituitary rises from the beginning of the cycle (early proliferation) towards its end (late secretion).* Lack of material has made it impossible to confirm this correlation further, or to investigate the premenstrual and menstrual phases of the cycle. — No other cell type in the anterior pituitary has been observed to vary definitely with the cycle in the 14 cases.

Hitherto, the structure of the human hypophysis has apparently not been observed to change with the menstrual cycle; such change has been observed in different animals, however. Thus, Rasmussen (1921) reported a pronounced increase in the number of basophiles in the pituitary of the woodchuck at the time for oestrus. In dogs and pigs, Wolfe and co-workers (cf. survey in Wolfe *et al.* 1932—33) found changed tingibility in the chromophiles and degranulation of the basophiles with the lutein phase. The most extensive investigations are probably on rats, however (Charipper and Haterius 1930; Reese 1932; Wolfe and Cleveland 1932—33; Wolfe 1934—35; cf. also surveys concerning different animals in Romeis 1940). In these animals Wolfe and co-workers found the most perceptible and statistically significant cyclic changes in the basophiles. Thus, the granulated basophiles had their maximum in prooestrus and their minimum in metoestrus, and 'non-granulated basophiles' their maximum in oestrus and minimum in prooestrus. It is difficult directly to compare the mentioned cyclic pituitary changes in animals with those demonstrated here in women. However, both the degranulation of the basophiles with the lutein phase in dogs and pigs, and the increase of the 'non-granulated basophiles' during oestrus in rats, seem to correspond to the raised frequency of hypertrophic amphophiles towards the end of the cycle in women.

Very little can be said with certainty on the significance of the observed cyclic change in the human anterior pituitary lobe. As degranulation of the basophiles can be induced in different animals by suitable dosage with most of the steroid

hormones (see survey of literature, above), the increased number of hyaline basophiles and hypertrophic amphophiles in the human pituitary towards the end of the cycle might be thought to be induced by the ovary's production of progesterone. Another possibility, according better with the histological character of these special cells, which points to strong function, is that their increase in frequency is linked up with an enhanced gonadotropic function, primarily a corpus-luteum-stimulating one. Particularly interesting is the fact that the mentioned frequency increase in women of fertile age may mean enhanced corticotropic function, for it is known that the adrenal cortex of the woman becomes broader and richer in lipoids towards the time for menstruation (cf. surveys in Anselmino *et al.* 1934, and von Lucadou 1935—36). As the number of cases in table 14 is far too small for a statistical analysis of the adrenal weight, it is not very interesting to know that in this material, too, the cases from the latter part of the cycle showed a greater adrenal weight (mean of 6 adrenals: 5.4 gm) than those from the earlier part (mean of 6 adrenals: 4.5 gm). It may be added that, of all the 20 women of fertile age investigated for positive PFR in the adrenal cortex, the only case to show such a reaction was the one with the greatest frequency of special cells in the anterior pituitary; this case was, at the same time, the one furthest advanced in the cycle (Case 14 in table 18; cf. coloured photos 19 and 20). Thus, there is nothing to contradict the view that the increased frequency of the special cells (hyaline basophiles + hypertrophic amphophiles) in the anterior pituitary of young women towards the end of the cycle may mean increased corticotropic function of the hypophysis; on the contrary, several observations point to this being so.

THE ADRENALS

Weight. The weight of the adrenal in the endocrinely normal men and women is shown in table 19. The results tally well with those submitted by most of the earlier investigators from — usually — fresh organs (cf. surveys in Dietrich and Siegmund 1926; von Lucadou 1935—36; Materna

Table 19. The weight of the fixed adrenal in normal men and women.

Men				Women			
Age in years	Number of cases	Number of adrenals	Weight in gm – Mean with standard error	Age in years	Number of cases	Number of adrenals	Weight in gm – Mean with standard error
16—19	1	2	3.8	16—19	2	4	5.4
20—29	2	4	4.9	20—29	3	6	5.5
30—39	1	2	6.1	30—39	5	10	5.2
40—49	9	18	5.6	40—49	2	4	4.7
50—59	12	24	6.1	50—59	5	10	5.9
60—69	15	29	4.8	60—69	10	20	5.3
70—79	7	14	5.5	70—79	8	16	5.8
80—89	1	2	4.0	80—89	4	8	4.5
90—99	0	0	—	90—99	1	1	3.1
18—46 Mean 38.3	13	26	5.39 (± 0.43)	17—46 Mean 28.5	11	22	5.31 (± 0.33)
50—81 Mean 63.0	35	69	5.36 ± 0.26	49—99 Mean 67.4	29	57	5.36 ± 0.27
64— 81 Mean 70.3	17	33	4.99 ± 0.33	64—99 Mean 74.6	19	37	5.18 ± 0.33
18—81	48	95	5.37 ± 0.22	17—99	40	79	5.34 ± 0.21

1942; Liebegott 1944). Like that of early investigators, this normal material also shows about the same values in men and women, and at different ages; possibly with some decrease towards old age, though the differences in table 19 are not statistically significant. The possibility of a decrease in weight towards old age has prompted the special calculation of the mean for 70-year-old men, since in this thesis the average age of the cases with prostatic hypertrophy, with which the values of the normal men are to be compared, is rather more than 70 years. Sources of error for the adrenal weight from infectious diseases, hypertonia, etc. will be discussed in connection with the comparison with the menopausal syndromes and prostatic hypertrophy.

It should be mentioned here and now, however, that the normal material in its entirety suggests a correlation between the frequency of the special cells in the anterior pituitary and the weight of the adrenal; cf. the women of fertile age. That

is to say, if we lump together the whole material of normal men and women whose anterior pituitary lobes have been differentially counted and whose adrenals have been weighed, we find that the adrenal weight seems to rise with the frequency of the special cells in the hypophysis. 19 such cases with more than 0.30 % special pituitary cells had an adrenal weight of 5.48 ± 0.28 gm; the remaining 8, with 0.30 % or fewer special pituitary cells had an adrenal weight of 4.79 (± 0.68) gm. A division with 0.35 % special cells as dividing-line gives the adrenal weights of 5.52 gm (11 cases) and 5.12 gm (16 cases) respectively. The material is so small, and the standard errors of the means so large and uncertain, that probably the only safe conclusion is that the findings do not argue against a positive correlation between the frequency of special cells in the hypophysis and the weight of the adrenal. Even this is of importance when comparing with the pathological groups, however.

The width of the adrenal cortex in the normal cases is shown in table 20. These values will also be discussed in more detail in the comparison with the pathological groups.

Table 20. Width of the adrenal cortex in normal men and women.

Nature and age of cases	Number of cases	Number of adrenals	Width of cortex in mm – Mean with stand. error
Men, 18—48 years	9	18	1.27
Men, 50—84 years, mean 63.6 years	14	28	1.21 ± 0.062
Women before menopause	17	34	1.40
Women in menopause, mean 65.2 years	25	49	1.32 ± 0.077

Ponceau-Fuchsin reaction. The results of the PFR in the normal cases are outlined in table 21.

As can be seen, the frequency of a positive reaction in the whole normal material is 15.9 ± 4.4 %. No difference can be made probable between men and women. It is also uncertain if the reaction is more often positive at a greater age. The difference between old and young is 15.6 ± 8.1 %, *i. e.* about

Table 21. The Ponceau-Fuchsin Reaction in the adrenal cortex of normal men and women.

	Nature of cases	Total number of examined cases	Ponceau-Fuchsin Reaction			Remarks
			Number of pos. cases	Number of doubtful cases	Number of neg. cases	
1.	Men 18—48 years . .	9	1	1	7	
2.	Men 50—81 years . .	15	5	2	8	
3.	Women before menopause 16—46 years	20	1	0	19	
4.	Women in menopause 41—99 years . . .	25	4	3	18	Of these 5 under 50 yrs. 1+ and 2?
5.	Total 1. + 3. = young persons	29	2	1	26	Difference in pos. cases 15.6 ± 8.1 %
6.	Total 2. + 4. = old persons	40	9	5	26	
7.	Total 5. + 6.	69	11	6	52	Total of pos. cases 15.9 ± 4.4 %

twice its standard error, if we calculate on the most unfavourable division. But even if the doubtful cases are divided up, the difference between the frequency of positive PFR in the young (2/29) and the old (11/40) will be 20.6 ± 8.5 %, *i. e.* probable but not significant. Sudds's finding (1940) of positive reaction in 24 % of the adult men and in 28 % of the adult women, the frequency rising with age, can probably be explained by the repeated occurrence of positive PFR in the menopausal syndromes and prostatic hypertrophy; see below.

OTHER ENDOCRINE ORGANS

Table 22 shows the weight of the epiphysis, the thyroid and the gonads in the endocrinely normal adults.

On comparison with reports from earlier investigators (cf. Henke-Lubarsch's Handb. d. path. Anat.), only two details in table 22 appear noteworthy, namely the high weight in the epiphysis of old women and the high thyroid weights of old men and women. The former figure is explained by the fact that 2 epiphyses with cysts up to the size of a pea were included among the 25 women aged 49—99 years. Apart from

Table 22. The weight of epiphysis, thyroid and gonads in normal men and women.

Nature of cases	Epiphysis	Thyroid	Gonads
Men, 18—48 years .	11 cases 0.158 g	13 cases 28.2	13 cases, 26 organs 14.3 g
Men, 50—84 years[1] .	26 cases 0.142±0.015 g	30 cases 31.1±2.94 g	28 cases, 56 organs 15.3±1.04 g
Women before menopause 16—46 years	5 cases 0.117 g	9 cases 29.4 g	8 cases, 16 organs 7.54 g
Women in menopause 49—99 years . . .	25 cases[2] 0.173 g (0.150±0.013 g)	24 cases 36.5±5.15 g	23 cases, 43 organs 2.25±0.20 g

[1] No clear difference for the weight of any organ at different ages.
[2] See the text.

these cases, the average epiphyseal weight in old women was 0.150±0.013 gm. The relatively high thyroid weights in old persons can probably be attributed to the inclusion of cases with (clinically atoxic) colloid struma.

The epiphysis was histologically examined in 25 normal cases, and was normal throughout, with the exception of simple cysts. In one case (59-year-old woman, O. 416/42) the thyroid showed slight morphological signs of raised function, namely moderate enlargement by nodules rich in colloid, epithelium high in places, sparse vacuolized colloid, and copious lymphoid tissue in the stroma. One case presented pronounced senile atrophy (99-year-old woman, O. 19/44). In the remaining 29 cases thus investigated, the thyroid was on the whole histologically normal.

The gonads were investigated histologically in 53 of the normal cases. They were histologically normal, apart from simple cysts or single persistent follicles and ordinary involutionary signs in the ovaries of the old women, and varying degrees of atrophy of the germinal tissue with fibrosis in the testes of the old men (pronounced in 2 cases, one with small lymphocyte infiltrates in one testis, the other with patches of slight hyperplasia of the interstitial cells). Concerning the fertile women, see above.

2. NORMAL CHILDREN

This comparison material has been compiled with the sole view of establishing the changes in the two girls with virilism (Cases 11 and 12) who are described in the next section — particularly the younger of these (Case 11). A corresponding material for comparison with the older children with the adrenogenital syndrome (Cases 9 and 10) has been considered unnecessary in view of the great changes of hypophysis and adrenals which they presented.

The 15 endocrinely normal children were chosen from subjects without clinical signs of endocrine disturbances or anatomical genital anomalies. As the two girls with virilism had bronchitis and broncho-pneumonia, normal cases with the same diseases have been chosen when possible (10 cases). Since, furthermore, the younger of the pathological cases had the clinical diagnosis of debilitas vitae congenita, and the elder vitium congenitum cordis, cases with these disorders have been included in the normal material (2 cases with debilitas vitae congenita, 1 case with vitium congenitum cordis, of the 15 normal cases). One of the normal cases showed simple cysts the size of a hazel nut in one adrenal; the adrenalsize of this case has therefore not been used in the investigation.

Weights. The average weight of the hypophysis was 144 ($\pm$ 16) mg in 9 children with the mean age of 61 days (6 boys and 3 girls, aged 4—150 days). A further 5 children with the mean age of 3.1 years had an average hypophyseal weight of 275 mg. The average adrenal weight of 8 children with the mean age of 49 days was 2.48 gm (6 boys and 2 girls, aged 1—150 days; 16 organs in all), with a standard deviation $\sigma = \pm 0.87$ gm. Needless to say, the value of σ is very uncertain, on account of the small number of cases. In the 5 older children (mean age 3.1 years), the adrenal weight was 1.87 gm. The values tally fairly well with those of earlier investigators (cf. Henke-Lubarsch's Handbuch, Vol. 8, 1926).

Table 23. Frequency of different cell types in the anterior pituitary of endocrinely normal children.

Case No.	Age in days	Sex	Frequency of different cell types in %									
			1. Acidophiles	2. Normal basoph.	3. Sparsely gran. basoph.	4. Total 2.+3.	5. Chromophobes with small nuclei	6. Chromophobes with large nuclei	7. Total 5.+6.	8. Hyaline basoph.	9. Hypertroph. amphoph.	10. Total 8.+9.
$^{429}/_{43}$	4	♂	15	1.4	4.1	5.5	69	10.	79	0.04	0.30	0.34
$^{137}/_{43}$	10	♀	15	3.3	2.3	5.6	74	5.0	79	0.03	0.15	0.18
$^{463}/_{43}$	63	♂	14	4.6	3.3	8.0	71	7.0	78	0.03	0.08	0.11
$^{478}/_{43}$	120	♀	16	2.1	3.5	5.6	71	7.2	78	0.05	0.14	0.20
$^{35}/_{44}$	150	♂	16	3.7	4.6	8.3	67	8.1	76	0.04	0.22	0.25
$^{19}/_{44}$	270	♀	24	3.6	4.9	8.5	65	3.0	68	0.04	0.19	0.24
Mean	103	3 ♂	16.7	3.1	3.8	6.9	69.5	6.7	76.3	0.04	0.18	0.22
$\pm\sigma$		+ 3 ♀	3.7	1.2	1.0	1.5	3.2	2.4	4.2	0.008	0.075	0.077

Histology of the anterior pituitary lobe. The results of the differential count of the anterior pituitary lobe in the children are shown in table 23.

The values in the table show good accordance from case to case. On the other hand, they deviate appreciably from those of Halpern (1938), the only author to make a quantitative investigation of the child hypophysis with satisfactory technique. Halpern used a method very like that of Rasmussen (see above), and found an average of 22.8—26.6 % acidophiles and 15.8—18.0 % basophiles in 88 full-term foetuses (54 males and 33 females). The values were rather larger in 16 children with ages ranging from some months to 14 years. It should nevertheless be mentioned that Halpern's values do not agree at all well with data by Staemmler (1915), Kraus (1926) and others, according to whom the basophile cells in the anterior pituitary lobe only appear at, or immediately after, birth. The different results may possibly be explained by differences in staining technique.

Besides the differential count, it was discovered that the basophile cells in the children were characterised by faintly ting-

ible granules, diffuse cellular outlines and small nuclei. The mulberry-like chalk concrements, described by Kraus (1912), were found in all the children.

The PFR in the adrenal cortex was clearly negative in all 6 children. This result agrees with those of Vines (Broster *et al.* 1938), and Sudds (1940).

3. THE ADRENOGENITAL SYNDROME

As the important questions bearing on this group of cases are concerned with comparisons between the morphology of the anterior pituitary lobe in Cushing's syndrome and in adrenal virilism respectively, the casuistic description will confine itself mainly to the hypophysis. Cases published earlier on by the present author will be briefly touched on.

In this group, the differential count of the anterior pituitary lobe was made only in the few cases where the pituitary changes were so slight that a quantitative investigation was required to establish them with certainty. The estimation method described above has been used in the remaining cases.

Case Reports

Case 1. Cushing's syndrome in 15-year-old girl.

(O. Lund 504/44. Autopsy: C. G. Ahlström, microscopic examination: the present author. Full clinical case report will be published by I. Nilsby, Lund.) — Previously healthy. Menarche at age of 13 years, menses subsequently regular. Obesity of 'buffalo type' increasing over 1 year and finally becoming enormous. Moon face and headache. Amenorrhoea suddenly set in about 9 months before death. She also gradually contracted pains in the back and right hypochondrium, purplish striae on thighs, breasts and flanks, osteoporosis, hypertonia, and pronounced polyglobulia. No hypertrichosis. Basal metabolism + 3 %. Blood sugar 0.09 %. Serum calcium 6.7, phosphorus 8.6, sodium 340, chlorides 346, and potassium 15 mg %. Prolan <67 and oestrone <17 MU/l urine. A tumour almost as large as a child's head was extirpated at the site of the right adrenal. The patient died a week later, after successive rise of temperature, and despite large doses of cortin.

Autopsy revealed normal pubes, tumorous infiltration in the retroperitoneal fatty tissue above the right kidney, tumorous invasion of the vena cava inf. with secondary thrombosis, multiple metastases in the lungs,

extreme fatty liver and moderate enlargement of the left half of the heart. No frontal enostoses were noted.

The hypophysis weighed 590 mg and was macroscopically normal. Microscopic examination of a sagittal section made near the centre. Htx-Magdala red (after fixing according to Susa). The anterior lobe showed moderate hyperaemia. No adenoma. The acidophiles were normal as to frequency and distribution, strikingly often with very small cellular bodies and small dense nuclei. There were very few chromophobes with small nuclei, probably much fewer than normally. Numerous chromophobes with large nuclei, possibly more than normally. Apparently no normal basophiles. Large quantities of typical hyaline basophiles and numerous typical hypertrophic amphophiles, with transitional types, all with large nuclei, poor in chromatin and often highly polymorphous. Transitional types between sparsely granulated basophiles and hypertrophic amphophiles were few. The hyaline basophiles predominated somewhat among the special cell forms. The special cells are plainly accumulated in common areas. Sparse colloid in the anterior lobe and in the boundary to the posterior lobe. The latter was free from basophiles, and normal generally.

The extirpated tumour from the site of the right adrenal: Weight 1 kg. Adrenocortical cancer with small necroses and negative PFR. — Left adrenal normal in size and shape. Cortex of usual width, very poor in lipoid, negative PFR. Ovaries of normal size, with abundant primordial eggs and normal follicular cysts, and some corpora albicantia. No corpora lutea or luteinisation of the stroma. — Uterus macroscopically normal. Uterine mucosa low, with regular, sparse glands as in early proliferation but with dense, round-celled, somewhat fibrous stroma. — Thyroid macro- and microscopically normal. — Pancreas macroscopically normal.

The hypothalamus was examined on frontal paraffin sections from the corpora mamillaria to the tuber region inclusive, stained according to Nissl. No material changes were observed in the subventricular and paraventricular centres (only part of the nuclei supraoptici was included in the sections, however).

Case 2. Cushing's syndrome in 16-year-old girl.

(O. SS., Gbg. A. P. Autopsy: G. Vejlens, microscopic examination: the present author. Published by the present author 1942.) — Previously healthy. Menarche at the age of 13 years. Ill for 9 months with amenorrhoea, moon face, slight obesity, specially on the abdomen, hypertrichosis of face and legs, cutaneous striae on abdomen and thighs, and acne, subsequently severe pyoderma. Hypertension and hypercholesterinaemia. No polyglobulia, normal values for blood sugar and blood calcium. — Stupor gradually set in, and the patient died from sepsis. — External genitals and pubes normal. No data as to calvaria or osteoporosis.

Hypophysis macroscopically normal. — Cut horizontally in an unbroken series, in 5 μ sections. Every 20th section examined in Htx-Magdala red.

— The anterior lobe showed moderate hyperaemia; in the anterior lower part there was an indistinctly demarcated accumulation, about 0.2 mm in diameter, of chromophobes with fairly large light nuclei and strips of acidophiles and hyaline basophiles. No circumscribed adenoma. — The acidophiles of the anterior lobe were numerous, normally distributed in the sections, usually with a remarkably small cellular body. The chromophobes were of normal quantity and size. Only a few normal basophiles. Typical hyaline basophiles very numerous. Here and there, particularly among the hyaline basophiles, were hypertrophic amphophiles with typical nuclei, poor in chromatin and often polymorphous. These were undoubtedly more numerous than normally. There were transitional forms between normal and hyaline basophiles on the one hand, and hypertrophic amphophiles on the other, though they were not many. — Slight basophile invasion in the posterior lobe, which was otherwise normal.

The adrenals were somewhat large, with broad cortex poor in lipoid. PFR negative. — Thyroid and parathyroid (1 found) macro- and microscopically normal. — Only fatty tissue at the site of the thymus. — Ovaries small, not gyrated or fibrotic. Cortex rich in primordial eggs. Some ordinary Graafian follicles and corpora albicantia. — Uterus small.

Case 3. Cushing's syndrome in 32-year-old woman.

(O. Sabb., Sthlm. 282/43. Clinical examination: R. Luft, examination of hypophysis: the present author, other pathological investigations Å. Lindgren. Published by Luft 1944, Case 17.) — Previously healthy. Symptoms of Cushing's syndrome for 7 years: irregular menses, with gradual appearance of amenorrhoea, moon face, pronounced torso obesity, moderate hypertrichosis in the face and linea alba, purplish striae, acne, osteoporosis, pains in the lumbar region, cervicodorsal kyphosis and increasing tiredness. Lowered glycose tolerance, hypercholesterinaemia, hypertonia. Signs of circulatory insufficiency, which were countered during her stay in bed. — Basal metabolism —7 to —31 %. Gonadotropin and oestrogen excretion in the urine lowered with repeated tests, androgen excretion (3—5 years after the beginning of the disease) usually high, on an average 25 mg/24 hours (Luft). — After 2 years' illness the syndrome was fully developed. Then followed an improvement for 2—3 months after extirpation of the left adrenal, which was normal as to size and shape. The patient then became worse, despite roentgen treatment of the hypophysis and large doses of Di-Menformon (oestradiol) 2 years before death, which resulted from suicide (sleeping draught).

The autopsy revealed no frontal enostoses. External genitals normal.

Hypophysis macroscopically normal. — Microscopic examination of a horizontal section made near the centre, Htx-Magdala red. — Anterior lobe hyperaemic. No adenoma. Here and there numerous leukocytes in the vessels, particularly eosinophile ones. The acidophile cells were normal or somewhat more numerous, normally distributed in the section. Many acido-

philes were quite small, with small dense nuclei. The chromophobes with small nuclei were possibly fewer than usual, those with large nuclei were normally numerous. Extremely few normal basophiles, rather more sparsely granulated basophiles. The section, and particularly the margins and anterior central part, is dominated by typical hypertrophic amphophiles with large nuclei, poor in chromatin and often polymorphous, together with a moderate though undoubtedly abnormal number of hyaline basophiles. Some of the latter were atypical, in that the cellular body was small and the contour not clear cut. There were numerous transitional forms between normal basophiles and the above-mentioned special cells, as also between the latter, appearing with plain topographical relationship. — Remarkably few and small colloid follicles on the boundary to the posterior lobe, which was free from basophile invasion, and normal in other respects.

The right adrenal contained a cortical adenoma the size of a thumb's end. The rest of the adrenal was very atrophic, with numerous cortical nodules hardly as large as a pin's head. PFR not investigated. — The extirpated left adrenal was histologically normal, with negative PFR. — Thyroid macro- and microscopically normal. — Parathyroids almost as large as pepper corns. — Ovaries the size of walnuts, with numerous follicular cysts and lutein cysts, and older corpora lutea. No luteinisation of the stroma. — Fat infiltration and arteriosclerosis in the pancreas; the islets seemed to be small.

Case 4. Cushing's syndrome with frontal enostoses in 40-year-old woman.

(O. SS., Gbg. 155/41. Autopsy: G. Vejlens, microscopic examination: the present author. Published by the present author 1942.) — Previously healthy. Amenorrhea for $\frac{1}{2}$ a year, and high fever for 2 months. Clinical signs of miliary TB, moon face, great adiposity, specially on the abdomen, striae on the thighs, hypertonia and hypercholesterinaemia. No polyglobulia or glycosuria. Prolan <40 MU/l urine (hormone laboratory, Lund). — At the autopsy the only noteworthy macroscopical finding was a distinct thickening of the calvaria in the frontal region, with nodulous inner surface, signs of pulmonary TB, pleuritis TB, general miliary TB and left-sided cardiac hypertrophy.

The hypophysis was macroscopically normal. — Microscopic examination after serial, horizontal 5 μ sectioning, every 20th section, Htx-Magdala red. — In the lower anterior lobe there was a basophile andenoma $5 \times 4 \times 3.5$ mm, with a few hyaline basophiles in the periphery. The acidophiles and chromophobes of the anterior lobe were normal as to frequency, structure and distribution. There were hardly any normal, and only few sparsely granulated basophiles in the anterior lobe, but plenty of hyaline basophiles and fairly few (though doubtless more than normal) hypertrophic amphophiles with typical nuclei; there were also transitional forms. The hypertrophic amphophiles were perceptibly accumulated among the hyaline basophiles. — Very little colloid. The posterior lobe had no basophiles, and was normal in other respects.

The adrenals had hypertrophic cortex poor in lipoid, with negative PFR. — The thyroid contained some tubercles but, like the parathyroids (3 found), was otherwise macro- and microscopically normal. — The ovaries gyrated, fibrotic, poor in primordial eggs and without corpora lutea; some miliary tubercles.

Case 5. Cushing's syndrome in 37-year-old man.

(O. Västerås 623/36. Autopsy: I. Behring, microscopic examination: the present author.) — Had earlier on suffered from duodenal ulcer. About a year before death he had a high facial colour and high blood values for erythrocytes. About 9 months before death he developed pains in the back and became increasingly tired; about 6 months later he showed enhanced thirst and glycosuria, which reacted well to insulin. Gradually contracted moon face, purplish striae, polyglobulia, moderate hypertonia, considerable osteoporosis (ribs, vertebrae and skull investigated with roentgen) and thoracic kyphosis. No obesity. Considerable loss of weight towards the end. Hormone assays (Lund) shortly before death: >18 but <55 MU oestrone and <17 MU prolan A per litre urine. — Roentgen irradiation of the pituitary region without perceptible effect. — Despite administration of adrenocortical extract, death after rise in temperature and signs of circulatory insufficiency about 24 hours after extirpation of a cancer twice the size of a fist from the site of the right adrenal.

Further autopsy findings: Invasion of a tumour thrombus in the vena cava inf., and slight cardiac hypertrophy.

Hypophysis macroscopically normal, weight 0.65 gm. — Microscopic examination of sagittal sections made near the centre, stained according to Mallory and with Htx-eosin. — General structure of the anterior lobe normal. No adenoma. Acidophiles normal as to frequency and distribution, often very small with small dark nuclei. Chromophobes with small nuclei rather scarce, those with large nuclei numerous. Very few normal basophiles; sparsely granulated basophiles somewhat more numerous, usually with very large and loose nuclei. The picture is dominated by very numerous typical hyaline basophiles; hypertrophic amphophiles relatively few; not many transitional types either between them or between basophiles and hypertrophic amphophiles. — Very large colloid follicles on the boundary of the posterior lobe, which was free from basophiles.

In view of the scarcity of hypertrophic amphophiles and their unclear topographical connection with other cell types in this case, the median section stained with Htx-eosin was subjected to a differential count according to Floderus, but in immersion enlargement. The frequency of the different cell types in 14 defined regions of the section were thus determined (for details, see Floderus 1944). The correlation between the frequency of hypertrophic amphophiles and acidophiles respectively was then calculated on the 14 pairs of values and, in the same way, the correlation amphophiles. —basophiles, etc.

Table 24. Frequency of different cell types in the anterior pituitary of Case 5 (37-year-old man with Cushing's syndrome) compared with that of normal men (means of 19, with average age 53.8 years). Only median sagittal sections.

Cases	Frequency of different cell types in %									
	1. Acidophiles	2. Normal basophiles	3. Sparsely granulated basoph.	4. Total 2.+3.	5. Chromophobes with small nuclei	6. Chromophobes with large nuclei	7. Total 5.+6.	8. Hyaline basophiles	9 Hypertroph. amphophiles	10. Total 8.+9.
Cushing V. $^{623}/_{36}$.	34.3	0.7	3.9	4.6	40.5	14.0	54.5	5.70	0.97	6.67
Normal men cf. tab. 16	23.3	12.6	5.4	18.1	52.1	6.1	58.3	0.039	0.35	0.39
Diff.	$+1.4\cdot\sigma$	$-1.5\cdot\sigma$	$-0.7\cdot\sigma$	$-1.7\cdot\sigma$	$-1.7\cdot\sigma$	$+\mathbf{3.2}\cdot\sigma$	$-0.5\cdot\sigma$	$+\mathbf{84}\cdot\sigma$	$+\mathbf{3.9}\cdot\sigma$	$+\mathbf{45}\cdot\sigma$

The results for the entire section are shown in table 24.

As can be seen, the total frequency of hypertrophic amphophiles is higher than normal, as also the frequency of chromophobes with large nuclei. The calculated correlations showed that only *one* correlation coefficient was significantly different from 0, namely that for the correlation between the hypertrophic amphophiles and normal basophiles: $r = + 0.65 \pm 0.16$. The frequency of the hypertrophic amphophiles was possibly positively correlated with the frequency of the hyaline basophiles: $r = + 0.36 \pm 0.23$, thus a better agreement with the other cases of the adrenogenital syndrome than the ordinary histological examination led one to expect.

Histologically, the adrenal tumour was a cortical adenoma in parts, and a typical cortical cancer in others. The PFR was uncertain, probably negative. The right adrenal was macroscopically normal; microscopically, it had a very even, narrow cortex (about 0.4 mm); PFR uncertain, probably negative. — Epiphysis macro- and microscopically normal; it weighed 0.07 gm. — The thyroid weighed 48 gm and showed histologically normal pictures. The pancreas was rather large, with small fatty tissue necroses in the cauda, but otherwise microscopically normal (Behring). — The site of the thymus was occupied by fatty tissue with quite small atrophic islands of thymus tissue without Hassall's bodies. — Testes rather small, and soft; microscopical atrophy of the germinative epithelium, no spermiogenesis. General moderate fibrosis in the form of coarse laminae propriae round the channels. The interstitial cells were normal in essentials.

Case 6. Cushing's syndrome in 50-year-old woman.

(Tmb. Lund 1628/43. Autopsy: O. Forssman, Kristianstad. Macroscopic investigation: C. G. Ahlström, microscopic examination: the present author.) — Patient had always had thoracic kyphosis. The menopause suddenly set in at the age of 47 years, about 2 years before death. For rather more than a year there had been increasing moon face, moderate adiposity of pronounced 'buffalo type', hypertrichosis in face and hands (otherwise normal female hair growth), tiredness, hypertonia, hyperglycaemia and possibly slight polyglobulia (5.13 million red blood corpuscles). No striae. Sometimes slight oedema in the lower legs. Basal metabolism normal. Died of pneumonia. Hormone assay (hormone laboratory, Malmö) about 3 months before death; at least 65 MU prolan A per litre urine.

Further autopsy findings: Cardiac hypertrophy (400 gm) and 'splenitis septica'.

The hypophysis was macroscopically normal. — Microscopic examination of a sagittal section made near the centre, Htx-Magdala red. — The general structure of the anterior lobe was normal. No adenoma. Acidophiles normal in frequency and distribution, many remarkably small, but otherwise normal. Chromophobes normal. Almost no normal basophiles, very few sparsely granulated ones. Typical hyaline basophiles very numerous, hypertrophic amphophiles and transitional cells between the last-named types fairly few, but undoubtedly more than usual. Very few transitional forms between sparsely granulated basophiles and hypertrophic amphophiles. The special cells mostly occurred together, particularly in the anterior part of the section; nevertheless, the topographical correlation was not specially marked. Fairly abundant colloid in the anterior lobe, here and there also in the form of drops in the vessels. Large colloid cysts on the boundary to the posterior lobe. The latter was invaded by a small number of basophiles and several typical hyaline basophiles; normal otherwise.

The adrenals were diffusely enlarged without adenoma; each weighed 15 gm. Microscopically the cortex was broad (about 2 mm), even, extremely poor in lipoid, with negative PFR (uncertain due to signs of autodigestion). — Thyroid rather large (50 gm), microscopically normal. — Pancreas: a scirrhous cancer in the cauda. The organ was otherwise normal on the whole. The islets possibly rather small. Possibly some increase of the A-cells in sections stained with azan (difficult to judge on account of autodigestion). — The uterus had a low mucosa with sparse glands, mainly regular and sometimes with slight cystic dilation, with inactive epithelium and somewhat fibrous stroma.

Case 7. Cushing's syndrome in 52-year-old woman.

(O. 399/42. Autopsy and microscopic examination: the present author.) — 5 normal pregnancies. Menopause at 40 years of age. From the age of 48 years there was increasing obesity, gradually becoming very great, of 'buffalo type', moon face, pronounced facial hypertrichosis, striae on the ab-

domen, strong osteoporosis (ribs, skull, vertebrae and sternum investigated), hypertonia, headache, signs of cardiac insufficiency, diabetes mellitus and polyglobulia. After no more than a year from the onset of the disease, the syndrome was fully developed, together with enlargement of the sella on roentgen films and lowered visual acuity. At the same time the blood cholesterine was 176 mg %; the blood calcium was 8.2 mg %, and subsequently 9 mg %. Basal metabolism normal. Repeated roentgen treatments of the pituitary region without definite effect. Died from cardiac insufficiency with lung oedema.

Further autopsy findings: Normal pubes, normal external genitals, thin calvaria without enostoses, cardiac hypertrophy and chronic stasis in the internal organs.

The anterior pituitary lobe was the site of a rounded tumour 25×20×18 mm, pressing the chiasma upwards. After fixing, the hypophysis with tumour weighed 9.45 gm. — Series of sagittal 5 μ sections; each 200th section (total: 19) investigated with Htx-Magdala red. In addition 2 sections made near the centre were stained according to Romeis (1940) and Crooke and Russel (1935). — The tumour consisted of a dense mosaic of polygonal cells with generally quite small, round or polymorphous nuclei and fairly sparse protoplasm. Most of the cells were amphophile and ungranulated (also in stainings according to Romeis and Crooke); over small areas, however, the cells were basophile, sometimes with plain basophile granulation. Thus, the tumour was a chromophobe-basophile adenoma. Part of the contour was sharp and marked by a thin capsule, but there was mostly no capsule against the rest of the anterior pituitary lobe which, together with the flattened posterior lobe, perched on the posterior-superior part of the adenoma like a $\frac{1}{2}$ mm thick cap. — The rest of the anterior pituitary lobe consisted of concentric cords of parenchyma cells in a rather coarser stroma than normal. The acidophiles seemed to predominate. They were mostly small, with small dense nuclei. The chromophobes were relatively few; otherwise normal. A moderate number of basophiles, most of them sparsely granulated. Hyaline basophiles in places, though probably not more than 0.5—0.75 %. Hypertrophic amphophiles more numerous, estimated at 2—3 % under the comparison microscope. Fairly few transitional types between both sparsely granulated basophiles and hypertrophic amphophiles, and between the different special cells. All types of parenchyma cells were apparently mixed haphazard. A few small colloid cysts on the boundary to the flattened posterior lobe, which was free from basophiles and normal in other respects.

The adrenals were of usual shape, very large; weight after fixing 12.6 and 11.4 gm. Cortex about 3.6 mm broad (in section); even, with moderate lipoid content in the peripheral third; otherwise poor in lipoid. PFR weakly positive bilaterally. Epiphysis macroscopically normal. — Thyroid weighed 16.5 gm (fixed); macroscopically normal, microscopically nodulous, with small follicles that had a mainly low but sometimes high cubic epithelium. The

colloid showed marginal vacuoles in parts, mainly red in Kraus specimens. Stroma normal. — Parathyroids all macroscopically normal (weights: 0.079, 0.064, 0.054 and 0.025 gm when fixed). All alike microscopically: Abundant interstitial fatty tissue, small atrophic bands of chief cells and groups of oxyphiles. In one of the glands there was a small group of water-clear cells. — Pancreas macro- and microscopically normal (van Gieson and gentian violet; silver staining after Gross-Schultze unsuccessful). — Ovaries small, 1.84 and 1.49 gm (fixed), greatly fibrotic, with some quite small persistent follicle cysts; no primordial eggs, corpora lutea or luteinisation of the stroma. Glycogen-stained liver sections showed numerous large parenchyma nuclei poor in chromatin, containing scales of glycogen.

Case 8. Cushing's syndrome in 53-year-old woman.

(O. Lund 450/43. Autopsy: C. G. Ahlström, microscopic examination: the present author.) — Signs of neurosis, increasing hypertension and cor hypertonicum incompensatum from her 44th year. Menopause at the age of 51 years. — About 1 year before death, when the patient was 52 years old, attacks of headache and pains in the lumbar region set in, and incipient moon face, adiposity and slight (subsequently inconstant) polyglobulia were noted for the first time (the patient had often been examined previously). She was treated inter alia with follidrine (oestrone: 4 doses of 100000 U. each). During the last year of life she gradually contracted typical moon face, pronounced adiposity of 'buffalo type', signs of osteoporosis (spontaneous rib fractures), purplish striae on abdomen and thighs, cutaneous suggillations and lowered glycose tolerance. Transient herpes zoster. During the last 2 months of life, she received roentgen treatment of the pituitary region. Died during increasing signs of cardiac insufficiency.

Further autopsy findings: Cardiac hypertrophy, lung oedema, osteoporosis in ribs and vertebrae, and multiple rib fractures, partly healed. No hirsutism.

The anterior pituitary lobe was the seat of a rounded tumour the size of a finger-end, of which a rounded portion the size of a hazel nut bulged up via a short, 1 cm broad connection towards the floor of the third ventricle behind the chiasma and in front of the corpora mamillaria. The hypophysis with tumour weighed 5 gm. — Microscopic examination of a sagittal section made near the middle line, Htx-Magdala red (after fixing according to Susa). — The tumour was built up of similar cells in a compact mosaic. The cell bodies were small, chromophobe, foamy or finely granulated, the nuclei rounded and small. The outer parts of the tumour were surrounded with a fibrous capsule, passing directly into the pituitary capsule. The tumour did not stand out clearly from the rest of the hypophysis, however. The remains of the anterior pituitary lobe, which formed a cap some mm broad on the posterior part of the adenoma, consisted of irregular cords of parenchyma cells in a denser stroma than usual. The acidophiles and chromophobes appeared normal as to frequency and appearance. Normal and sparsely granulated basophiles had a fairly normal frequency, most

numerous towards the boundary of the adenoma. Here and there in the anterior pituitary remains, particularly towards the adenoma boundary, there were numerous typical hyaline basophiles and fairly numerous hypertrophic amphophiles (undoubtedly pathological quantities). Transitional types were few between hyaline basophiles and hypertrophic amphophiles, and fairly few between granulated basophiles and hypertrophic amphophiles. The special cells were not strictly confined in common areas. — Colloid sparse. The posterior lobe was flattened with moderate invasion of both normal and hyaline basophiles.

The adrenals were very large, together weighing 41 gm (before fixing). The cortex was broad, about 2 mm in the sections, with some demarcated adenomas of at most 1.2 mm in diameter. The sparse lipoids of the cortex were unevenly distributed. PFR negative bilaterally. — Ovaries small, 1.9 gm each (after fixing), gyrated, fibrotic, without primordial eggs, follicles, corpora lutea or luteinisation of the stroma. — The uterus mucosa measured about 1.2 mm; presented slightly irregular glands, sometimes with slight cystic dilation, and showing inactive epithelium but loose, spool-celled stroma without thrombi or necroses.

Case 9. Transitional case between Cushing's syndrome and precocious puberty in 7-year-old boy.

(O. Sabb., Sthlm 192/40. Clinical investigation: R. Luft, autopsy: H. Bergstrand, microscopic investigation: the present author. Published by the present author 1942, and by Luft 1944, Case 26.) — Previously healthy. Increasing adiposity confined to the torso during 4—5 months. Moon face, pubes, slight hair on the upper lip, penis large for his age. Hypertension and acne. No polyglobulia, hyperglycaemia or osteoporosis. — Died 2 days after the extirpation of a left-sided adrenal tumour twice as large as a fist. — According to Luft, the excretion of gonadotropin was <40 MU/l urine, that of androgens was 131.5—151.5 mg/day, and that of oestrogens 20 IU/day.

Hypophysis macroscopically normal. Microscopic examination of sagittal sections made near the centre, stained with Htx-Magdala red and according to Kraus. — Anterior lobe somewhat hyperaemic. No adenoma. Acidophiles normal as to structure, frequency and distribution, usually with fairly small bodies and nuclei. Chromophobes with small nuclei probably few, those with large nuclei numerous. Normal basophiles extremely few; rather more sparsely granulated basophiles with large nuclei poor in chromatin. The picture was dominated by typical hyaline basophiles, rather fewer hypertrophic amphophiles, and numerous transitional types between them, as also between sparsely granulated basophiles and hypertrophic amphophiles. Very pronounced topographical connection between the hypertrophic amphophiles and the hyaline basophiles. — Little colloid in the anterior lobe and on the boundary to the posterior lobe. Very slight invasion in the latter by normal basophiles. (Cf. fig. 2.)

The adrenal tumour was histologically a typical adrenocortical cancer with large necroses and haemorrhages. PFR uncertain, probably weakly positive, in that quite few and small groups of cells with fuchsinophile granules were observed in the scanty preserved tissue portions.

For other details, see Luft (1944), who maintains inter alia that the right adrenal was oedematous (not examined histologically).

Case 10. Precocious puberty in 7-year-old boy.

(NP. 23/39. Autopsy: G. Vejlens. Microscopic investigation: the present author. Published by the present author 1942.) — Born 3 weeks late(?), normal delivery, weight at birth 3370 gm, normal measurements. During the first year of life the mental and physical development was normal. From the age of 1 year, proportional gigantism became more and more manifest: weight at 1 year: 12.25 kg; at 2 years: 15.6 kg; at 4 years 1 month: 25.8 kg, height: 128 cm. Weight at 4 years 4 months: 27.4 kg, height 130 cm; pubes beginning to grow, penis 7.5 cm, testes the size of hazel nuts, voice deeper than normal, mental development that of a 4-year-old. Motoric disturbance, basal metabolism +34 %, glycose tolerance normal. No hypertonia or other symptoms of Cushing's syndrome. — Died suddenly from pneumonia at the age of $7\,^{3}/_{4}$ years.

Autopsy findings: Child very large for his age, looks like a 15-year-old. Height: 170 cm; proportions good. Hair on the genitals and underarms as in puberty. Brain large, weighing 1675 gm. — Pneumonia crouposa. — No symptoms of Cushing's syndrome, no epiphyseal tumour.

Hypophysis macroscopically normal. — Microscopic examination of horizontal sections made near the centre, stained with Htx-Magdala red, according to Kraus (1914) and according to Crooke and Russel (1935). — General structure of the anterior pituitary lobe normal. No adenoma. Acidophiles numerous, on the whole normally distributed in the sections, but more abundant than normally in the front of the lobe. Chromophobes in usual numbers. Normal basophiles very few, sparsely granulated basophiles in normal or increased numbers, particularly in the central and front part of the sections. The nuclei of all the cell types mentioned varied remarkably in size, being often unusually large and loose. Rather many hyaline basophiles, particularly in the front border of the sections. Only a few fully typical hyaline basophiles; the rest had either diffuse cell outlines, small nuclei, or only small hyaline fields. Some of them formed transitional forms to hypertrophic amphophiles, which were fairly numerous, particularly in the central and front parts of the section, and which often had very large polymorphous nuclei. Transitional types between sparsely granulated basophiles and hypertrophic amphophiles were fairly few. Thus, the special cells were far more abundant than normally.

The adrenals were considerably enlarged, weight: 33 and 18 gm. The cortex was hypertrophic, creased like a morel or cerebral gyri, 2—2.5 mm broad, poor in lipoid. Atrophic marrow. Strongly positive PFR in all coats

of the cortex bilaterally. — Thyroid macroscopically normal. — Large thymus, weight 40 gm; otherwise macroscopically normal. — Testes large as at puberty, weighing 13 gm each.

Case 11. Virilism in 41-day-old girl.

(O. 408/43. Autopsy and microscopic examination: the present author.) — Born at term, normal delivery, weight at birth: 3000 gm. Breast-fed. There was gradual loss of weight, with attacks of cyanosis and diarrhoea, ending in death. — Malformation of the external genitals was observed even at birth. On the day before she died she was given 1000 IU ovex (oestrone) to provoke the menses, which would establish the presence of a uterus; streaks of blood in the urine on the evening before death. Clinical diagnosis: Debilitas vitae congenita + Hermaphroditismus externus.

Autopsy: Weight 2840 gm, normal habitus, normal flesh. No pubic, axillary or facial hair. Labia majora normal. Clitoris as large as the penis of a newborn boy; well-developed glans with a shallow depression in the tip, and prepuce. The cm-long vagina of normal width opened jointly with the urethra into a mm-wide orifice immediately behind the base of the clitoris. Uterus, tubes and ovaries normal. No prostate (section series of urethra-vagina specimens). No testes, epididymes or vasa. — Cranial bones normal. — Bronchitis capillaris and broncho-pneumonia.

Hypophysis macroscopically normal. Weight (fixed): 150 mg, *i. e.* normal when compared with the normal material. — Microscopic examination and differential count according to the author's own method, described above. For results, see table 25.

Table 25. Frequency of different cell types in the anterior pituitary of Case 11 (41-day-old girl with virilism) compared with that of normal children (means of 6, with average age 103 days).

Cases	Frequency of different cell types in %									
	1. Acidophiles	2. Normal basophiles	3. Sparsely granulated basoph.	4. Total 2.+3.	5. Chromophobes with small nuclei	6. Chromophobes with large nuclei	7. Total 5.+6.	8. Hyaline basophiles	9. Hypertroph. amphophiles	10. Total 8.+9.
Virilism $^{408}/_{43}$	16.1	1.2	13.0	14.2	52.7	16.1	68.9	0.19	0.66	0.84
Normal cases cf. tab. 23	16.7	3.1	3.8	6.9	69.5	6.7	76.3	0.04	0.18	0.22
Diff.	$-0.2\cdot\sigma$	$-1.6\cdot\sigma$	$+\mathbf{9.2}\cdot\sigma$	$+4.9\cdot\sigma$	$-5.3\cdot\sigma$	$+3.9\cdot\sigma$	$-1.8\cdot\sigma$	$+\mathbf{19}\cdot\sigma$	$+\mathbf{6.4}\cdot\sigma$	$+\mathbf{8.1}\cdot\sigma$

This case of virilism is admittedly somewhat younger than the average for the normal control cases. However, as is shown by a comparison with table 23 and with the literature data on increasing frequency of basophiles with age, this should *lower* the differences found rather than anything else. In table 25 these differences have been expressed as multiples of σ for the respective cell type in the normal material. It is true that the values for σ are very unreliable on account of the smallness of the material, but it should be possible to regard differences of more than $6 \cdot \sigma$ as trustworthy. It is then found that the virilism case shows an increase of sparsely granulated basophiles, hyaline basophiles and hypertrophic amphophiles, and probably an increase in the total frequency of basophiles, together with a decrease of chromophobes with small nuclei.

As well as the count, it was also established that the basophiles consistently showed very large cell bodies for the age of the subject, and as a rule very large nuclei, poor in chromatin. These changes dominated the picture of the anterior lobe with low magnification. Transitional forms were fairly numerous between sparsely granulated basophiles and hypertrophic amphophiles, and fairly few between the special cells. The acidophiles had a normal structure. The distribution of the different cell types to different areas, as in the normal children, was not marked. The special cells were also scattered, without any plain connection with one another. — No adenoma. — Very little colloid. Posterior lobe normal.

Adrenals very large, 7.1 and 6.5 gm (after fixing); the mean for the cases was therefore 6.8 gm. The difference from normal weight of 2.48 (8 cases, 16 organs, $\sigma = \pm 0.87$ gm, cf. p. 88) is thus $5 \cdot \sigma$ and may well be considered significant, despite the smallness of the material, since it must not be forgotten that the observed normal weight agreed well with that of earlier investigators. — The adrenal cortex was not particularly broad, but was crumpled as a morel or cerebral gyri, extremely poor in lipoid, with strongly positive PFR. — Epyphysis macroscopically normal. — Thymus normal for the age both macro- and microscopically, as also the thyroid and parathyroids (2 found). — Pancreas macroscopically normal; microscopic investigation revealed numerous islets, otherwise nothing noteworthy found in van Gieson and azan staining. — Ovaries macroscopically normal, weight (fixed): 0.103 and 0.112 gm. Microscopic examination: Narrow medullary zone, cortex rich in primordial eggs and a few follicles, the largest 1×0.6 mm. No corpora lutea, no atretic follicles or corpora albicantia. — Uterus mucosa normal for the age. — Vaginal mucosa invested with non-cornified squamous epithelium, in several layers.

Case 12. Mongolism and incipient precocious puberty (?) in 9-month-old girl.

(O. 117/43. Autopsy and microscopic investigation: the present author.) — Born at term, normal delivery, weight at birth 2880 gm. Signs of mongolism, vitium congenitum cordis and pyloro spasm. Vomiting about every

other day, hypotonia in the joints, slow development, apathetic. Died after rise in temperature.

Autopsy findings: Unusually small for her age, thin. Round face with slightly slanting eyes, suggestions of epicanthus. Short overarms and fingers. The distal phalanges of the little fingers deviated radially. Normal hair on the head; plain growth of hair on the labia majora and mons pubis with clear-cut upper limit; no axillary or facial hair. External genitals otherwise normal. Base of the skull unduly ossified for her age (?), the clivus seemed long. — Cardiac septum defect, supernumerary pulmonary lobes, bronchitis, broncho-pneumonia bil., otitis media acuta bil., meningitis acuta suppurativa, gastritis chronica and hypertrophia muscularis ventriculi.

Hypophysis macroscopically normal. — Microscopically examined after a series of sagittal 5 μ sections, each 100th section stained with Htx-Magdala red. Differential count of the anterior lobe of 3 sections according to the author's own method. — Result of the count is shown in table 26.

Table 26. Frequency of different cell types in the anterior pituitary of Case 12 (270-day-old girl with incipient precocious puberty) compared with that of normal children (means of 6, with average age 103 days).

Cases	Frequency of different cell types in %									
	1. Acidophiles	2. Normal basophiles	3. Sparsely granulated basoph.	4. Total 2.+3.	5. Chromophobes with small nuclei	6. Chromophobes with large nuclei	7. Total 5.+6.	8. Hyaline basophiles	9. Hypertroph. amphophiles	10. Total 8.+9.
Prec. pub. $^{117}/_{43}$ . . .	7.1	4.6	3.5	8.1	70.3	13.7	84.0	0.07	0.69	0.76
Normal cases cf. tab. 23	16.7	3.1	3.8	6.9	69.5	6.7	76.3	0.04	0.18	0.22
Diff.	$-2.6\cdot\sigma$	$-1.3\cdot\sigma$	$0.3\cdot\sigma$	$+0.8\cdot\sigma$	$+0.3\cdot\sigma$	$+2.9\cdot\sigma$	$+1.8\cdot\sigma$	$+3.8\cdot\sigma$	$+\mathbf{6.8}\cdot\sigma$	$+\mathbf{7.0}\cdot\sigma$

The differences from the means of the normal cases has been expressed in σ in the same way as in Case 11. Only the hypertrophic amphophiles permit an anything like definite assessment: they were pathologically increased in number. — In addition to the count, it was found that the general structure of the anterior lobe was normal, no adenoma. Acidophiles normal. Transitional types were rare between hyaline basophiles and hypertrophic amphophiles, and fairly rare between sparsely granulated basophiles and hypertrophic amphophiles. No marked predilection of any one cell type for any one area. No colloid. One section of the series presented a slight

but distinct basophile invasion in the posterior lobe, which was otherwise normal.

The adrenals were of normal size for the age. The cortex was of ordinary width with numerous adenomas the size of rice-grains, poor in lipoid. PFR negative with the exception of a few fuchsinophile cells in an adenoma. — Epiphysis, thyroid and thymus macro- and microscopically normal. — Parathyroid (1 found) macroscopically normal, microscopically built up of only water-clear cells in dense mosaic. — Pancreas macroscopically normal. Azan stain revealed almost no A-cells in the islets; otherwise microscopically normal. Ovaries macroscopically normal. The microscope revealed large quantities of primordial eggs, several ordinary follicles, the largest 2.5 mm in diameter, no corpora lutea or corpora albicantia. — Uterus macro- and microscopically normal.

Case 13. Virilism in 37-year-old woman.

(O. 84/38. Autopsy and microscopic examination: the present author. Published by the present author 1942). — Previously healthy. Ill for 3 1/2 years: Metrorrhagias, gradually amenorrhoea and signs of metastasising tumour in the right adrenal tract. After being ill 2 1/2—3 years, she gradually contracted a deeper voice, coarser features, facial hypertrichosis, pubes of pronounced male type and slight clitoric hypertrophy. No clinical symptoms of Cushing's syndrome; highest weight: 67 kg. No hypertonia or glycosuria. Died after losing much weight.

Further autopsy findings: Cholelithiasis, no osteroporosis, calvaria normal.

Hypophysis macroscopically normal. — Microscopic examination of horizontal sections made near the centre and stained with Htx-Magdala red, according to Kraus (1914), Wallart and Houette (1934), and after Crooke and Russel (1935). — Anterior lobe loose, no adenoma. Acidophiles normal in frequency, distribution and structure, though a number of them had strikingly small cellular bodies. Chromophobes fewer than normally, particularly those with small nuclei; they were distributed as usual in the sections. Normal basophiles extremely few, occurring above all in the anterior central part of the sections. Sparsely granulated basophiles scarce. The picture was dominated by hypertrophic amphophiles with very large nuclei, poor in chromatin and often very polymorphous, particularly in the front and peripheral parts of the section. (Fig. 3). The hyaline basophiles were fairly few (but unquestionably more than normally); seldom fully typical, in that many had partly amphophile, foamy protoplasm, thus forming transitional types between hyaline basophiles and hypertrophic amphophiles. These two cell types showed a marked predilection for one another, and were found in the regions where the basophiles are normally most numerous. There were not many transitional types between sparsely granulated basophiles and hypertrophic amphophiles. — Small amount of colloid. Posterior lobe almost free from basophiles (of normal appearance), and otherwise normal.

At the site of the right adrenal there was an adrenocortical cancer, oval, 21 × 16 × 11 cm, weighing 2130 gm (making it the largest adrenocortical cancer ever reported; cf. Anderson *et al.* 1943). It was histologically of characteristic structure, with large haemorrhages and necroses. PFR positive. Numerous metastases in different organs. — Left adrenal macroscopically normal with profusely developed marrow, narrow cortex, poor in lipoid, and some quite small cortical nodules. PFR negative. — Epiphysis, thyroid and pancreas macro- and microscopically normal, though the thyroid was somewhat smaller than usual. — Parathyroids not enlarged. — Ovaries gyrated, fibrotic, very poor in primordial eggs. Two follicle cysts filled with blood. No corpora lutea or luteinisation of the stroma. — Uterus mucosa atrophic.

Case 14. Virilism in a 48-year-old woman.

(O. 289/40. Autopsy: A. Eurelius; microscopic investigation: the present author. Published by the present author 1942.) — Ill 10 months: Amenorrhoea, voice gradually becoming deeper, increasing and finally pronounced hypertrichosis of face and arms and legs, but normal female pubes. Blood pressure 155/105 mm Hg. Towards the end there were abdominal striae, but no other signs of Cushing's syndrome. Signs of metastasising adrenal tumour. Died after increasing tiredness and loss of weight.

Further autopsy findings: Coarse features; nothing mentioned about the external genitals, calvaria, or bone system otherwise. Cholelithiasis and signs of chronic gastritis.

Hypophysis macroscopically normal. — Microscopic examination of horizontal section made near the centre, stained with Htx-Magdala red. — General structure of the anterior lobe normal, no adenoma. Acidophiles normal as to frequency and distribution, many with normal structure, not a few with moderately enlarged nucleus, poor in chromatin. Probably fewer chromophobes than normally, particularly those with small nuclei. Normal basophiles very few, sparsely granulated basophiles numerous — possibly more than normally. The basophiles were distributed as usual in the section. Numerous hypertrophic amphophiles, usually with moderately polymorphous nuclei, poor in chromatin. Hyaline basophiles not particularly plentiful, but without doubt considerably more than normally; as a rule they were not very large and had only small hyaline fields, but were otherwise typical (fig. 4). Sparse occurrence of transitional types between hyaline basophiles and hypertrophic amphophiles; these types numerous between sparsely granulated basophiles and hypertrophic amphophiles. The specials cells most often lay together within the basophile regions. — Little colloid. The posterior lobe contained quite few basophiles of normal structure, and was otherwise normal.

On the site of the left adrenal there was a typical adrenocortical cancer twice the size of a fist, with necroses, haemorrhages and positive PFR.

Numerous metastases in lungs and lymphatics of the neck. The remains of the left adrenal, and the right adrenal, showed normal cortex, with moderate lipoid content and small circumscribed nodules in the capsule; PFR negative in the cortex bilaterally. — Epiphysis and pancreas macroscopically normal. — Thyroid macro- and microscopically normal. — Parathyroids not enlarged. — Ovaries small, gyrated, fibrotic without primordial eggs, follicles or corpora lutea.

Case 15. Virilism and frontal enostoses in 74-year-old woman (transitional case between adrenogenital syndrome and syndroma Morgagni).

(O. 111/42. Autopsy and microscopic examination: the present author. Published by the present author 1942.) — Previously healthy. Treated 1 year for dacryocystitis. Hypertonia. Was finally given large doses of sulfathiazol. Died from uraemia. Virilism symptoms not investigated clinically.

Autopsy findings: On the whole normal habitus, with normal musculature. Not fat, but the flesh was mainly localised at the trunk; fore-arms and lower legs lean. No moon face, striae or osteoporosis (ribs and vertebrae examined). Frontal enostoses the size of a pea. Very strong facial hypertrichosis, heavy pubes of pronounced male type, slight but unquestionable clitoric hypertrophy with well-developed prepuce. — Also hypoplasia of the right kidney, chronic glomerulonephritis, haemorrhagic double broncho-pneumonia, and acute dermatitis.

Hypophysis macroscopically normal. — Microscopic examination of horizontal sections made near the centre and stained with Htx-Magdala red, according to Kraus (1914), Wallart and Houette (1934), and to Crooke and Russel (1935). — General structure of the anterior lobe normal, no adenoma. Acidophiles considerably fewer than normally, normal in structure and distribution. Possibly fewer chromophobes with small nuclei; those with large of ordinary frequency. Distribution of the chromophobes normal. Normal and — in particular — sparsely granulated basophiles perceptibly more numerous, often with nuclei poor in chromatin, and ordinarily distributed in the sections. Hyaline basophiles very plentiful; often typical with large nuclei poor in chromatin. Moderate number of transitional types to hypertrophic amphophiles; few typical hypertrophic amphophiles, on the other hand (though more than normally). Moderate number of transitional types between sparsely granulated basophiles and hypertrophic amphophiles. The special cells showed a predilection for each other and for normal basophiles. — Extremely little colloid in the anterior lobe and on the boundary to the posterior lobe. The latter showed an enormous invasion of normal and sparsely granulated basophiles, but was free from sure hyaline basophiles, and was otherwise normal.

Adrenals of normal shape, the right considerably enlarged ($8 \times 4 \times 0.8$ cm), the left of normal size. The cortex on both sides was fairly narrow, poor in lipoid, and with clearly positive PFR in the form of numerous groups

of fuchsinophile cells. — Thyroid macro- and microscopically normal in all essentials. — Parathyroids (2 found) macro- and microscopically normal. — Pancreas macroscopically normal. Microscopic examination useless on account of autodigestion. — Typical left-sided tubo-ovarian cyst, the size of a walnut. Ovaries small, gyrated, fibrotic, without primordial eggs or corpora lutea. Each showed several persistent follicles half as large as a pea. — Uterus macroscopically normal. Uterus mucosa fibrotic, with single, cystically dilated glands with inactive epithelium.

Case 16. Virilism in 42-year-old woman.

(O. Basel 575/42. Autopsy: J. Wallart; Microscopic examination of hypophysis and adrenal tumour: the present author.) — Only available data: 'Virilism' and 'adrenal cancer' (J. Wallart).

Hypophysis examined histologically on 5 μ sagittal sections made near the centre and stained with Htx-Magdala red, according to Wallart and Houette (1934) and according to a modified Masson's trichrome method (Wallart 1939), all after fixing according to Duboscq-Brasil. — Anterior lobe hyperaemic. No adenoma. Acidophiles often very small, of usual distribution in the sections. Chromophobes of ordinary structure, basophiles often with large nuclei, normally distributed. Hyaline basophiles (often typical), hypertrophic amphophiles, and transitional forms between the two were very frequent, as also intermediate types between sparsely granulated basophiles and hypertrophic amphophiles. However, in contrast to the situation in most of the other hypophyses in this material, this case presented no clear topographical correlation between the frequency of hypertrophic amphophiles and the frequency of basophiles or hyaline basophiles. The Htx-Magdala red section was therefore subjected to a differential count according to Floderus in immersion enlargement (cf. above, Case 5). The frequency of different cell types for the whole section is shown in table 27; for purposes of comparison the table includes means for the sagittal median sections of the 29 normal women. As seen, the observations as to the cell frequencies were borne out at the count: the special cells, and particularly the hyaline basophiles, had greatly increased.

The calculations of the correlations between the frequency of hypertrophic amphophiles and the frequency of other cell types within the 14 regions of the section yielded only *one* correlation coefficient greater than 2.5 times its standard error, namely that for the correlation between the frequencies of hypertrophic amphophiles and chomophobes with large nuclei. This correlation coefficient was $+ 0.73 \pm 0.12$. On the other hand, the frequency of hypertrophic amphophiles was not correlated with either that of the basophiles or that of the hyaline basophiles. It could therefore be confirmed that this case formed an exception as regards the distribution of the hypertrophic amphophiles within the anterior pituitary lobe.

There was little colloid in the anterior lobe and on the boundary to the

Table 27. Frequency of different cell types in the anterior pituitary of Case 16 (42-year-old woman with virilism) compared with that of normal women (means of 29, with average age 48.3 years). Only median sagittal sections.

Cases	Frequency of different cell types in %									
	1. Acidophiles	2. Normal basophiles	3. Sparsely granulated basoph.	4. Total 2.+3.	5. Chromophobes with small nuclei	6. Chromophobes with large nuclei	7. Total 5.+6.	8. Hyaline basophiles	9. Hypertroph. amphophiles	10. Total 8.+9.
Virilism Ba. $^{575}/_{42}$.	16.2	1.9	11.4	13.3	48.1	20.7	68.8	0.63	1.11	1.75
Norm. women cf. tab. 16	26.7	9.2	6.6	15.8	48.3	8.8	57.2	0.038	0.30	0.34
Diff.	$-0.9\cdot\sigma$	$-1.7\cdot\sigma$	$+2.0\cdot\sigma$	$-0.5\cdot\sigma$	$-0.02\cdot\sigma$	$+2.7\cdot\sigma$	$+1.1\cdot\sigma$	$+11\cdot\sigma$	$+5.4\cdot\sigma$	$+8.8\cdot\sigma$

posterior lobe. Very slight invasion of the posterior lobe by sparsely granulated basophiles.

The sections of the adrenocortical tumour showed a typical adrenocortical cancer. PFR negative.

Summary and Commentary

Diagnosis of the cases

There can only be doubt as to the diagnosis in one of the 16 cases with the adrenogenital syndrome, namely Case 12. — This case, a 9-month-old girl with mongolism, showed precocious puberty only by perceptible pubes of feminine type. Although there were no signs of virilism, it is probable that the case should be interpreted as adrenogenital sexual precocity, as the negative morphological findings for all endocrine organs except the adrenals (and the hypophysis) argue plainly against any other genesis, but are well compatible with the adrenal genesis (cf. survey of literature). On the other hand, the diagnosis can hardly be backed up by the numerous adrenocortical small adenomas, for such are not unusual in children (cf. Broster *et al.* 1938, and others); the PFR was positive

only in one small adenoma, and therefore of little value as proof. The diagnosis therefore remains uncertain.

The other 15 cases are typical exponents of all the most usual forms of the adrenogenital syndrome, as a comparison between the survey of the literature and table 28 shows. Thus, 9 cases present Cushing's syndrome, and 7 cases show pronounced virilism symptoms (other than merely facial hypertrichosis), 1 (No. 9) including both the clinical syndromes mentioned; all with concurrent hyperplasia or cancer of the adrenal cortex. For the rest, the symptom complexes varied somewhat in typical fashion in each group. It should be specially stressed that there were frontal enostoses in 2 cases; thus, Case 4 showed Cushing's syndrome simultaneously with Morgagni's syndrome, and Case 15 showed marked adrenal virilism simultaneously with Morgagni's syndrome.

THE HYPOPHYSIS

Macroscopical structure. Macroscopically, the hypophysis was normal except for 2 cases with large adenomas of the anterior lobe. In these 2, the weight exceeded the normal range of variation, but lay within it in the 2 further cases where this factor was determined.

Adenoma in the anterior lobe was observed in only 3 of the 16 cases, all 3 with Cushing's syndrome: Case 4 showed a small basophile adenoma, Case 7 a large mixed chromophobe-basophile adenoma, and Case 8 a purely chromophobe adenoma. Serial sectioning of the anterior lobe further demonstrated absence of adenoma in one of the cases with Cushing's syndrome (No. 2), thereby confirming the conclusion, advanced in the survey of the literature, that pituitary adenomas are not essential to the adrenogenital syndrome. On the other hand, the results do not contradict the earlier experience that basophile adenomas in the anterior pituitary lobe are more usual in Cushing's syndrome than in normal subjects (cf. survey of the literature); in this material, adenomas with basophile cells was observed in 2 cases of 9 with Cushing's syndrome, but only in 2 cases of 72 normal subjects.

Histological structure. The results of the cell frequencies in the anterior lobe are in direct opposition to those reported by several earlier investigators (without satisfactory methods of comparison, cf. Malaguzzi-Valeri 1940), to the effect that simple basophile hyperplasia is usual in Cushing's syndrome. In this material none of the 9 cases with Cushing's syndrome showed even the suspicion of an increase in the total number of granulated basophiles; of the 8 cases with virilism, only 1 (No. 15) showed a sure increase of this kind and 1 (No. 11) a probable one when compared with hypophyses of normal cases of corresponding sex and age. On the other hand, the total frequency of granulated basophiles was perceptibly lowered in 7 of the Cushing cases (including Case 9), and in 3 of the virilism cases (including Case 9). In view of the smallness of the material, we can only conclude that simple hyperplasia of the basophiles of the anterior pituitary is not characteristic of either Cushing's syndrome or adrenal virilism.

On the other hand, it is very likely that a simple degranulation of the basophiles belongs to the distinguishing features of the anterior pituitary lobe in the adrenogenital syndrome, whether this latter takes the clinical form of Cushing's syndrome or of virilism. That is to say, 12 of the 16 cases showed a perceptible relative increase of the number of sparsely granulated basophiles in relation to the number of normally granulated basophiles. Nor do the 4 remaining cases argue against the conclusion in point, for in 2 of them (Nos. 1 and 2) the frequency of both normal and sparsely granulated basophiles was too low to be satisfactorily determinable by the comparison microscope; the assessment in the 3rd case (No. 8) was upset by a large adenoma, and in the 4th case (No. 12) the clinical symptoms suggested only a slight disturbance.

The main changes in the anterior pituitary both in Cushing's syndrome and in adrenal virilism proved to concern hyaline basophiles and hypertrophic amphophiles. As table 28 shows, all 16 cases of the adrenogenital syndrome were characterised by a usually very strong pathological increase of these special

cell types (though very doubtful as regards the hyaline basophiles in Case 12).

Nevertheless, there seems to be a certain difference between Cushing's syndrome and adrenal virilism without Cushing symptoms, in that the anterior pituitary picture is dominated by the hyaline basophiles in most cases of the former group, and by the hypertrophic amphophiles in most cases of the latter. This difference is not regular, however, since the hypertrophic amphophiles preponderated in 2 cases of typical Cushing's syndrome (Cases 3 and 7), and the hyaline basophiles in 1 case of virilism (No. 15). It is therefore very doubtful if the difference in question has any direct correlation with the difference between the clinical picture of the two groups.

On the other hand, it is very likely that the preponderance in the adrenogenital syndrome of one or other of the special cell types of the anterior pituitary lobe is linked up with the duration of the disease. The duration is known for 12 of the 16 cases with the adrenogenital syndrome (Cases 11 and 12 are omitted because they are infants and therefore not directly comparable with the others; the period of disease is not known for Cases 15 and 16). We then see that, of the 8 cases with less than 2 years' disease (7 with Cushing's syndrome, 1 with virilism) 7 show plainly more hyaline basophiles than hypertrophic amphophiles in the anterior pituitary lobe; but in the 4 with more than 3 years' illness (2 with Cushing's syndrome, 2 with virilism), there is no preponderance of hyaline basophiles, but on the other hand 3 of them show a marked preponderance of hypertrophic amphophiles (2 with Cushing's syndrome, 1 with virilism). — These results agree as regards Cushing's syndrome with those of Gellerstedt (1939), the first and — apart from the present author — the only one who has hitherto registered the hypertrophic amphophiles in this disease. In 2 such cases with about 1 year of disease, Gellerstedt found an abundance of typical hyaline basophiles, together with varying numbers — yet fewer — of hypertrophic amphophiles (Cases I and II), but in a 3rd case with between 6 and 10 years' illness he found fewer hyaline basophiles in the remaining part of the anterior lobe outside a basophile adenoma (p. 253);

finally, in a 4th case with a 10-year period of disease, he found quite few typical hyaline basophiles, but more such in the 'atrophic final stage' outside a mixed adenoma (p. 253, Case Bergstrand, 1934).[1]

The present author has had the opportunity of subsequently investigating hypophysis sections from the two last-mentioned Cushing cases (Gellerstedt's 3rd and 4th cases). In the 3rd case there was an abundance of typical hypertrophic amphophiles; these were admittedly fairly few in the 4th case, but they were assuredly more than the typical hyaline basophiles.

It is true that Gellersedt did not advance the direct proportion between the quotient

$$\frac{\text{frequency of hypertrophic amphophiles}}{\text{frequency of hyaline basophiles}}$$

and the duration of the disease, which his material thus shows, but he nevertheless (on purely morphological grounds) drew the correct conclusion that the hypertrophic amphophiles probably express late functional stages of the hyaline basophiles (cf. also above, survey of the literature).

This confirms the present author's earlier observation (1942; cf. survey of the literature above) that *Cushing's syndrome and adrenal virilism are characterised by the same change in the anterior pituitary lobe, i. e. a — usually very strong — increase of hyaline basophiles and hypertrophic amphophiles and — in all probability — by a concurrent simple degranulation of the basophile cells.* The quantitative variation of the anterior pituitary cells from case to case, *i. e.* the preponderance of now one, now the other of the two special cell types, is

[1] The time of disease for the 3rd case is not given in Gellerstedt's paper but has been taken from the corresponding clinical record, autopsy No. 327/38. Demonstration by Gellerstedt has made it clear that the 'hyaline basophiles in the atrophic final stage' consist of quite small cells with small, usually dense nuclei, partly hyaline and most often partly foamy protoplasm, often with peripheral remains of basophile granules — thus, an atrophic counterpart to 'transitional types between hyaline basophiles and hypertrophic amphophiles' according to the nomenclature in this thesis. It may be added that the present author has not seen atrophic cell types of this kind in other cases.

probably connected rather with the duration of the disease than with its clinical form of Cushing's syndrome or virilism.

Apart from the changes mentioned, no regular deviations from the normal were observed in the anterior pituitary lobe in the adrenogenital syndrome. However, numerous small acidophiles — usually with small, dense nuclei — appeared relatively often (9 cases of 16); in 7 cases of 9 with Cushing's syndrome, and in 3 cases of 8 with virilism (cf. table 28). In the normal subjects, the small acidophiles appeared in abundance only in 4 cases of 48. Thus, the difference from the normal material in this respect is fairly significant for Cushing's syndrome (difference + 69.5 ± 14.4 %) and very uncertain for virilism (difference + 29.2 ± 17.6 %). We cannot, however, draw the general conclusion that small acidophiles are found more frequently in Cushing cases than in virilism cases (difference + 40.3 ± 22.0 %). The only permissible conclusion is that numerous small acidophiles are often but not regularly found in the anterior pituitary lobe in Cushing's syndrome; the situation in virilism as regards them is not certain.

A secondary finding, finally, is that two of the Cushing cases (Nr:s 6 and 8) showed several hyaline basophiles among the basophiles invading the posterior lobe. The significance of this observation will be touched on later.

THE ADRENALS

Medullary deviations from the normal were noted in only 1 case, in which the marrow was atrophic (No. 10).

The adrenal cortex was hyperplastic in 8 cases, the seat of a large adenoma in 1, the seat of quite small multiple adenomas (normal?) in 1, and of cancer in 6 cases. There was no difference as regards the macroscopic changes between cases with Cushing's syndrome and those with only virilism symptoms; this agrees with earlier experiences (cf. table 28 and survey of the literature).

The lipoid content of the cortex was noted in 12 cases. It was low in 10 (5 Cushing's syndrome, 5 virilism) and normal in 2 (1 Cushing's syndrome, 1 virilism).

The PFR was strongly positive in 2 cases, both of them children with virilism (cf. table 28). The reaction was positive in a further 3 cases with virilism and in 1 case of Cushing's syndrome; it was questionable in 2 virilism cases. There can therefore be no doubt that the reaction is more often positive in virilism than in the normal material (virilism cases including 2 infants: 8 cases with 5 positive, of which 2 were strongly positive; normal material including 6 infants: 75 cases with 11 positive, of which none were strongly positive). It is similarly plain that positive PFR is not a characteristic of Cushing's syndrome (1 positive case of 9). It has been maintained that, owing amongst other things to the difficulty of 'reading off' the reaction, its result can be regarded as trustworthy only in the form of means for larger groups, but not in the individual case (cf. above, chapter on methods). Therefore, a doubtful or negative reaction in some of the virilism cases is no indication that the function which it expresses is not essential to adrenal virilism. Thus, the results tally well in all parts with those of Vines (Broster, Vines *et al.* 1933, 1938), which wer discussed above.

OTHER ENDOCRINE ORGANS

These organs showed no regular changes either in Cushing's syndrome or in virilism. However, atrophy of the gonads often occurred in the adults of both categories (fibrosis of the ovaries in 7 cases, atrophy of the testicular germinative tissue without hyperplasia of the interstitial cells in 1 case). Thus, the results agree with earlier experiences (cf. survey of the literature).

The hypothalamus was investigated in a Cushing case, without its being possible to demonstrate changes (apart from some small fresh bleedings).

IMPORTANCE OF THE PITUITARY CHANGE IN THE ADRENOGENITAL SYNDROME

With regard, first, to the origin of the hypertrophic amphophiles, it could be confirmed that transitional types between these cells and hyaline basophiles occurred in varying quanti-

Table 28. Survey of the cases with the adrenogenital syndrome.

In the table, 'Virilism' denotes precocious puberty or unmistakable signs of virilism other than facial hirsutism. — The signs concerning the pituitary cells denote pathological increase. — 'Correlation A.-H.' indicates topographically common occurrence. — A blank square means no record.

Case	Clinical symptoms					Anterior pituitary					Adrenal cortex		Atrophy of gonads
	Obesity	Facial hirsutism	Hypertension	Other symptoms of Cushing's s.	Virilism	Adenoma	H. Hyaline basoph.	A. Hypertroph. amphophil.	Correlation A.—H.	Small acidophiles	Macroscopically	PFR	
1. 15 years ♀[1]	+	—	+	+	—	—	+++	++	+++	+	Cancer	—	
2. 16 » ♀	+	+	+	+	—	Series —	++	+	++	+	Hyperplasia	—	—
3. 32 » ♀	+	+	+	+	—	—	++	+++	++	+	Adenoma	—	—
4. 40 » ♀[2]	+		+	+	—	Baso-phil.	++	+	++	—	Hyperplasia	—	+
5. 37 » ♂	—		+	+		—	+++	+	(+?)	+	Cancer	(—?)	+
6. 50 » ♀	+	+	+	+	—	—	+++	+	+	+	Hyperplasia	—	
7. 52 » ♀	+	+	+	+	—	Mixed Chromo-phob.	+	++	—	+	»	+	+
8. 53 » ♀[3]	+	—	+	+	—		+	+	+	—	»	—	+
9. 7 » ♂	+	+	+	+	+	—	+++	++	+++	+	Cancer	(+?)	
10. 7 » ♂	—	—	—	—	+	—	++	++	++	—	Hyperplasia	++	(—?)
11. 41 days ♀	—	—	—	—	+	—	++	++	—	—	»	++	
12. 9 months ♀	—	—	—	—	(+)	Series —	(+?)	++	—	—	Normal?	(+?)	
13. 37 years ♀	—	+	—	—	+	—	+	+++	+++	(+)	Cancer	+	—
14. 48 » ♀	—	+	(+)	—	+	—	+	++	++	—	Cancer	+	
15. 74 » ♀[2]	—	+	+	—	+	—	++	+	++	—	Hyperplasia	+	
16. 42 » ♀					+	—	++	++	—	+	Cancer	—	

[1] Hypothalamus normal.

[2] Frontal enostoses.

[3] Hyaline basoph. in the post. lobe.

ties in all the cases of the adrenogenital syndrome. Similarly, transitional types between sparsely granulated basophiles and hypertrophic amphophiles were regularly found. This has further strengthened the morphological grounds for assuming that the latter cells are developed from the basophiles — in part, at least, via the hyaline change.

A study of the distribution of the hypertrophic amphophiles in the sections showed that, in 11 of the 16 cases with the adrenogenital syndrome, these cells showed a plain predilection

for the hyaline basophiles in those areas where normal basophiles are usually preponderant (cf. table 28). In a 12th case (No. 5) this topographical connection was not pronounced with the hyaline basophiles, but was certain as regards normal basophiles. In a further 3 cases the topographical investigation provided no definite data, since all cell types were 'mixed' (Cases 7, 11 and 12). Only in 1 case of the 16 (No. 16) did the hypertrophic amphophiles occur without topographical correlation with the basophiles (or hyaline basophiles), but with a positive correlation of this kind with another cell type (chromophobes with large nuclei). This exception is hard to explain, since this very case showed unusually many transitional types between normal and hyaline basophiles on the one hand and hypertrophic amphophiles on the other. However, it is conceivable that in Case 16, unlike the others, the development of basophiles into hypertrophic amphophiles took place with different intensity in different regions of the anterior lobe, so that the normal and hyaline basophiles were used up where the hypertrophic amphophiles were most numerous, but were not consumed where the latter cells remained few.

As to the remaining 15 cases, showing positive topographical correlation between basophiles (normal or hyaline) and hypertrophic amphophiles, this correlation can, on the other hand, only imply one of the following three possibilities: 1) Basophiles develop into hypertrophic amphophiles with on the whole the same intensity in all parts of the anterior pituitary lobe (during possible regeneration of the basophile granules at a uniform rate in different areas of the lobe). 2) Other cells, normally found mainly among the basophiles, similarly develop into hypertrophic amphophiles. These other cells might be chromophobes (judging from the topographical report of Floderus in 1944). However, this possibility is improbable, since the hypertrophic amphophiles in several of the cases with the adrenogenital syndrome were perceptibly more abundant among the basophiles than among the chromophobes. 3) Other cells, normally most abundant where the basophiles are few, *i. e.* acidophiles (Floderus 1944), develop into hypertrophic ampho-

philes, but do this selectively, and preferably in those areas where the basophiles are many. This possibility is obviously improbable.

Thus, the morphological criterion can be supplemented by both the topographical and the chronological criterion, namely the above-mentioned fact that the hyaline basophiles are often fewer, and the hypertrophic amphophiles often relatively more, after long illness than after short. Taken all together, these circumstances indicate very plainly that, *in the adrenogenital syndrome, the hypertrophic amphophiles develop — at any rate in large measure — from the basophiles, probably in part via the hyaline change.*

As regards the connection of the pituitary change with the clinical symptoms in the adrenogenital syndrome, we have already pointed out the fundamental fact that the increase of the special cells, *i. e.* the hyaline basophiles and the hypertrophic amphophiles seem, with basophile degranulation, to be common to Cushing's syndrome and virilism without Cushing symptoms. In point of fact, no appreciable variation of this pituitary change has been noticed in the presence of different symptoms within the adrenogenital group (cf. table 28). Nor has it been possible to show any correlation between the pituitary change and any change in other endocrine organs (or the hypothalamus), with the exception of the adrenal cortex. It may be considered established that the adrenocortical changes observed (cortical hyperplasia, adenoma or cancer, as also positive PFR) in the adrenogenital syndrome form the anatomical background to a hyperfunction (cf. above, survey of the literature). It is therefore extremely likely that the demonstrated change in the anterior pituitary lobe either expresses the direct cause or is the direct consequence of the hyperfunction of the adrenal cortex in the adrenogenital syndrome.

4. THE MENOPAUSAL SYNDROMES

THE HYPOPHYSIS

Weight. The weight of the hypophysis was determined in 11 cases with menopausal syndromes, including 1 man with

Syndroma Morgagni; the average age of the 11 cases was 65.1 year, and the weight of the hypophysis (mean with standard error) 976 (± 113) mg. Taking only the 10 women, the average age was 67.1 years and the weight of the hypophysis 1009 (± 119) mg. For 29 normal women in the menopause with an average age of 67.9 years, the weight of the hypophysis was 827 ± 22 mg, and for 35 normal men with an average age of 63.1 years it was 741 ± 20 mg (cf. table 11). Thus, no statistically significant differences in the weight of the hypophysis can be shown between the pathological and the normal groups. The high mean for the former nevertheless suggests that high values for the hypophysis may be commoner in the menopausal syndromes than normally. In any case, the figures do not argue atrophy of the hypophysis in these syndromes.

Cell frequencies in the anterior pituitary. The results of a differential count of the anterior pituitary lobes of 18 cases with menopausal syndromes are given in table 29. The 18 cases included a man with frontal enostoses (and also diabetes mellitus). As, in this case, the frequency values for the different anterior pituitary cells did not appreciably differ from those of the other 17 cases, the group has been treated as homogeneous and been compared with normal women in the menopause with a corresponding age distribution. The comparison shows (cf. table 29) that, in the menopausal syndromes, the anterior pituitary is primarily characterised by an increase in the number of sparsely granulated basophiles and of hypertrophic amphophiles, as also — in all probability — of hyaline basophiles, though this last is not constant (difference of the mean from that of the normal cases is about 2.8 times its standard error; difference for the total of the special cells from that of normal cases 6.5 times its standard error). Furthermore, it seems clear that an increase of the total number of basophiles is typical of the menopausal syndromes (difference from the normal value 3.0 times its standard error), and so, possibly, is a decrease in the number of chromophobes with small nuclei (difference from the normal

Table 29. Frequency of different cell types in the anterior pituitary of cases with menopausal syndromes (including 1 man with frontal enostoses).

For comparison, corresponding values of normal women in the menopause (cf. also tables 13 and 14).

Case No.	Age in years	Sex	Frequency of different cell types in %									
			1. Acidophiles	2. Normal basophiles	3. Sparsely granul. basophiles	4. Total 2. + 3.	5. Chromophobes with small nuclei	6. Chromophobes with large nuclei	7. Total 5. + 6.	8. Hyaline basophiles	9. Hypertrophic amphophiles	10. Total 8. + 9.
215/43	42	♀	17	9.0	13	22	48	12	60	0.11	0.47	0.58
14/44 [1]	45	♂	38	5.3	7.5	13	35	14	49	0.13	0.54	0.67
97/43	51	♀	33	4.5	9.6	14	35	17	52	0.14	0.67	0.82
219/43	61	♀	19	6.0	5.3	11	55	14	69	0.21	0.55	0.77
104/43	62	♀	27	7.4	8.4	16	43	13	56	0.02	0.55	0.57
252/43	64	♀	34	6.8	9.1	16	37	12	49	0.19	0.31	0.50
341/43	64	♀	33	12	4.9	17	42	8.3	50	0.03	0.45	0.48
425/42	66	♀	29	7.1	7.0	14	48	8.6	56	0.03	0.53	0.56
54/43 [2]	66	♀	32	8.7	8.2	17	42	8.8	51	0.06	0.46	0.52
25/44	67	♀	24	11	8.0	19	45	11	56	0.03	0.53	0.56
399/43 [3]	69	♀	22	12	13	25	37	16	53	0.53	0.34	0.87
183/43 [4]	71	♀	31	14	10	24	30	13	44	0.13	0.77	0.89
450/42	72	♀	36	9.1	8.8	18	38	8.0	46	0.08	0.49	0.56
479/43 [4]	73	♀	29	11	7.1	18	39	13	53	0.00	0.67	0.67
170/43	78	♀	30	13	6.8	20	37	12	49	0.06	0.69	0.74
192/44 [5]	78	♀	22	27	4.3	32	44	1.4	45	0.50	0.13	0.62
165/43	79	♀	24	4.9	9.2	14	45	16	61	0.09	0.61	0.70
422/42 [5]	85	♀	28	18	12	30	33	8.1	41	0.68	0.13	0.80
Menopausal syndromes, 17 ♀ + 1 ♂			28.2 ±	10.4 ±	8.5 ±	18.9 ±	40.7 ±	11.5 ±	52.2 ±	0.17 ±	0.49 ±	0.66 ±
Mean 66.3 yrs. $M \pm \varepsilon(M)$			1.38	1.29	0.59	1.36	1.47	0.89	1.61	0.046	0.042	0.031
Normal women Mean of 15: 68.1 years $M \pm \varepsilon(M)$			31.1 ± 1.40	8.4 ± 0.86	5.7 ± 0.61	14.1 ± 0.85	46.2 ± 1.61	8.3 ± 1.00	54.5 ± 1.69	0.04 ± 0.011	0.30 ± 0.038	0.34 ± 0.038
Difference $D \pm \varepsilon(D)$			− 2.9 ± 1.97	+ 2.0 ± 1.55	+ **2.8** ± 0.85	+ **4.8** ± 1.60	− 5.5 ± 2.18	+ 3.2 ± 1.34	− 2.3 ± 2.33	+ 0.13 ± 0.047	+ **0.19** ± 0.057	+ **0.32** ± 0.049

[1] Also diabetes mell.; small anaemic necrosis in ant. pit.

[2] Ant. pit. cut in series; no adenoma.

[3] 1 mixed and 1 acidophile adenoma in ant. pit.

[4] Also diabetes mell.

[5] Hyaline basophiles in post. lobe too.

value 2.5 times its standard error). A less pronounced probability (difference from the normal value more than 2.3 times its standard error) suggests an increase of the number of chromophobes with large nuclei, also.

Table 30 presents the differentially counted material supplemented by the 23 further cases where the frequency of the special cells (hyaline basophiles and hypertrophic amphophiles) was only estimated by the comparison microscope. For purposes of comparison, the table also includes corresponding material of normal women in the menopause. As is seen, the total material confirms the fact that the special cells of the anterior pituitary lobe appear with a high frequency far more often in the menopausal syndromes than in normal women.

Table 30. Occurrence of the special cells in the anterior pituitary of cases with menopausal syndromes compared with that of normal women in the menopause.

Combined material of hypophyses differentially counted and examined under the comparison microscope. Cf. tab. 15.

Nature of cases	Age in years, mean	Total number of examined cases	Frequency of the special cells		
			Number of cases with > 0.55 %	Number of doubtful cases	Number of cases with < 0.55 %
Menopausal syndromes 42—85 years	65.1	41	27 65.9 %	6 14.6 %	8 19.5 %
Normal women in menopause 41—99 years[1]	65.8[1]	24	1 4.2 %	2 8.3 %	21 87.5 %
Difference, $D \pm \varepsilon(D)$ in %	—	—	+ 61.7 ± 8.46	+ 6.3 ± 7.89	— 68.0 ± 9.16

[1] In 3 cases the age is unknown.

It might be questioned whether the changes in cell frequency demonstrated above really are essential to the menopausal syndromes, although there seem to be certain exceptions. After all, the differentially counted material of menopausal syndromes represented values less than the mean for the normal cases in 3 cases for the sparsely granulated basophiles, in 5 cases for hyaline basophiles, and in 2 cases for hypertrophic ampho-

philes (cf. table 29). The deviations downwards from the corresponding normal means are admittedly small as a rule, but may well be significant for the hypertrophic amphophiles in 2 cases (O. 192/44 and 422/42), and possibly for the hyaline basophiles in 1 case (O. 479/43 in table 29; cf. above concerning the standard error of the mean of a single case). Objections based on these findings have little weight, however. For one thing, the value for the total of the special cells (hyaline basophiles + hypertrophic amphophiles) in each of the differentially counted cases of the menopausal syndromes are obviously higher than the corresponding normal mean, though they are very high (more than 0.55 %) in only 65.9 % of all the cases (table 30). Also — and above all — it is probable that cytological changes such as those demonstrated may, in the individual case vary very rapidly with the intensity of the functional derangement they express; needless to say, the functional derangement may be essential to the group in its entirety, even if separate cases showed it to be less intensive than the average at the time of investigation.

Thus, the anterior pituitary is characterised in the menopausal syndromes by degranulation of the basophiles and increase of the number of special cells (hyaline basophiles and hypertrophic amphophiles); that is to say, by the same change as that found in the adrenogenital syndrome, though less pronounced quantitatively. However, the menopausal syndromes also show a clear increase of the total number of basophiles, a change which is not characteristic of the adrenogenital syndrome. The menopausal syndromes are possibly also characterised by an increase of the chromophobes with large nuclei.

Figs. 6 and 7 show characteristic anterior lobe pictures of cases with menopausal syndromes.

The importance of the pituitary change, and its correlations with clinical symptoms, will be discussed below. It may, however, be stated here and now that, in the group with menopausal syndromes, the cases with and the cases without internal frontal enostoses have on the whole shown the same anterior lobe picture. It is therefore possible to make a comparison with the results of earlier investigators concerning

both 'Cushingoid habitus' and Syndroma Morgagni. Support has been found both for Reider's observation (1937, 1938) of an increased number of hypertrophic chromophobe cells in the anterior pituitary lobe of a single case of Syndroma Morgagni, and for the observation of the present author (1942) of pituitary pictures in 'Cushingoid habitus', Syndroma Morgagni and the adrenogenital syndrome, all resembling one another. To a certain extent, Henschen's observation (1937) of a simple basophile hyperplasia in the anterior lobe in Syndroma Morgagni, and Gellerstedt's supposition (1939) that a hyperplasia of this kind is typical of 'Cushingoid habitus', have also been confirmed. However, the analogy which Henschen and Gellerstedt claimed *on these grounds* to have found between the menopausal syndromes and Cushing's disease hardly holds water. Nor could Henschen's finding (1937) of an increased number of acidophiles in Syndroma Morgagni be confirmed.

The results of the present author do not agree very well with the observations of Floderus (1944), who made a differential count of the anterior lobe in 3 cases with Syndroma Morgagni and 5 control cases of older women, for Floderus found no difference in frequency in either acidophiles, basophiles or chromophobes between the two groups. However, his material is a bit small to allow of definite conclusions.

Observations concerning the structure of the hypophysis, by the side of the differential count. Adenomas (1 mixed chromophobe-basophile and 1 acidophile) were observed in the anterior lobe of 1 case of the 41 with menopausal syndromes, as against 4 cases of the 72 normal cases (adult men and women). Serial sectioning of the anterior pituitary lobe was admittedly made on only 1 of the negative cases, but as at least 3 pituitary sections through different parts of the anterior lobe were examined in 16 of the remaining 39 cases, it can definitely be said that adenomas are not characteristic of the menopausal syndromes.

Small acidophiles were not noted in any of the 18 differentially counted cases with menopausal syndromes. The difference in this respect from the normal material (4 cases of 48) is

Table 31. Basophile invasion and colloid content in the hypophysis of cases with menopausal syndromes compared with those of normal women in the menopause. — Cf. tab. 17.

Nature of cases	Age in years, mean	Total number of examined cases	Basophile invasion of neurohypophysis			Colloid content		
			slight	moderate	strong	slight	moderate	strong
Menopausal syndromes 42—85 years	65.9	29	15 51.7 %	7 24.1 %	7 24.1 %	9 31.0 %	14 48.3 %	6 20.7 %
Normal women in menopause 41—99 years	67.6	19	11 57.9 %	1 5.3 %	7 36.8 %	6 31.6 %	11 57.9 %	2 10.5 %
Difference, $D \pm \varepsilon(D)$ in %	—	—	-6.2 ± 14.6	$+18.8 \pm 9.5$	-12.7 ± 13.6	-0.6 ± 13.7	-9.6 ± 14.6	$+10.2 \pm 10.3$

obviously not probable; on the other hand it is probable as compared with Cushing's syndrome (difference: 77.8 ± 13.9 %).

Table 31 shows the occurrence of basophile invasion in the neural lobe and of colloid in the anterior lobe (including the boundary region to the neural lobe) in the menopausal syndromes.

As is seen, the values agree very well with those in the normal material; the greater frequency of 'moderate basophile invasion' in the menopausal syndromes can at most indicate a smaller dispersion in this material than in the normal material.

Finally, the menopausal syndromes also showed invasion by hyaline basophiles in the posterior lobe, with a small number of atypical examples in one case (O. 422/42), and with several typical examples in one case (O. 192/44). See below.

The origin of the hypertrophic amphophiles. As in the normal cases and those with the adrenogenital syndrome, the cases with menopausal syndromes could always be found to show transitional cell types between the hyaline basophiles and hypertrophic amphophiles in the anterior pituitary, when the hyaline basophiles were fairly numerous; transitional types between normal basophiles and hypertrophic amphophiles occurred regularly. The transitional forms were often plentiful.

In the menopausal syndromes, too, the hypertrophic amphophiles occurred plainly accumulated in the basophile regions (in 17 cases of 18); this topographical correlation was very pronounced in 5 cases. Only in 1 case of the 18 were there numerous hypertrophic amphophiles among the acidophile cells also (O. 104/43). When the hyaline basophiles were fairly plentiful, they regularly appeared together with the hypertrophic amphophiles. *Doubtless, therefore, the menopausal syndromes also see the development, at all events in large measure, of the hypertrophic amphophiles from the basophiles, probably in part via the hyaline change.*

THE ADRENALS

Weight and cortical breadth. The weight of the adrenal was determined in 20 cases (39 organs) of menopausal syndromes aged 42 to 93 years (mean age 65.0 years). The mean weight was 6.39 ± 0.40 gm. The corresponding value of 57 adrenals from 29 normal women in the menopause with a mean age of 67.4 years was 5.36 ± 0.27 gm (cf. table 19). The difference is thus $+ 1.03 \pm 0.48$ gm, *i. e.* about 2.1 times its standard error. The probability that the difference is conditioned by chance is therefore less than 4: 100. In the normal material the mean weight of the adrenal was the same in both old men and old women (table 19). For comparison purposes it is therefore legitimate to make these groups into one, which then have a common mean (for 64 cases, 126 organs; average age 65.0 years) of 5.36 ± 0.18 gm. The difference between the adrenal weight in cases with menopausal syndromes and this common normal value is 1.03 ± 0.44, *i. e.* more than 2.3 times its standard error. Thus, there is only a 2: 100 probability that the abnormally large weight which this material shows in the adrenals in the menopausal syndromes is conditioned by chance.

Even normally, the cortex constitutes about 90 % of the adrenal volume, and the marrow only about 10 % (von Lucadou 1935—36; Liebegott 1944). If, therefore, the demonstrated increase in the adrenal weight of cases with menopausal syndromes was due to a hyperplasia of the marrow, this should

have been evident macroscopically. No such medullary hyperplasia has been observed; on the other hand, a perceptible cortical hyperplasia has been macroscopically visible in most of the cases with high adrenal weight. We can therefore conclude that the observed means for the weight reflect the size of the cortex.

The breadth of the adrenal cortex was determined in 41 cases with menopausal syndromes (aged 42—85 years; mean age 65.2 years), and was 1.70 ± 0.14 mm. In 25 normal women in the menopause (41—99 years; mean age 65.2 years), this breadth was 1.32 ± 0.077 mm. The difference is thus $+ 0.38 \pm 0.16$ mm, *i. e.* rather over 2.3 times its standard error, corresponding to a probability for chance of 2: 100. Thus, the measurements of the cortical breadth were also unable to *establish* adrenocortical hyperplasia in the menopausal syndromes.

However, the measurements of the cortical breadth have been extensively made *on other cases* than those where the adrenal weight was determined. In the 22 cases with menopausal syndromes where the adrenal weight was not determined (mean age 66.8 years), the cortex was 1.77 ± 0.23 mm broad; in the 16 normal women in the menopause, also with undetermined adrenal weight (mean age 62.3 years), it was 1.34 ± 0.096 mm. The difference between the last-mentioned groups was thus $+ 0.43 \pm 0.25$ mm, *i. e.* rather over 1.7 times its standard error, making a 9: 100 probability of a random difference. This latter difference in the adrenocortical breadth and the above difference in the adrenal weight (with a probability of chance of 2: 100) between menopausal syndromes and normal cases, represent two sides of the same thing, and the differences have been established quite independently of one another. The probability that both the differences are contingent on chance is thus only $\frac{9}{100} \cdot \frac{2}{100} = \frac{18}{10000}$. In other words, it has been statistically established that *the adrenocortical hyperplasia observed in the menopausal syndromes in this material is not due to chance.*

However, what has been said above does not immediately

Table 32. Influence of infection on adrenal weight.

Cases of the menopausal syndromes compared with normal women in the menopause with corresponding average age.

Nature of cases	Weight of the adrenal (gm) in cases		
	without infection	with acute infection	with chron. infection
Menopausal syndromes 42—93 yrs (includ. 1 man)	11 cases, 21 adrenals 5.77	6 cases, 12 adrenals 5.98	3 cases, 6 adrenals 9.37
Normal women in menopause 49—99 yrs	14 cases, 28 adrenals 5.54	9 cases, 18 adrenals 4.88	6 cases, 11 adrenals 5.69
Difference	+ 0.23	+ 1.10	+ 3.68

prove that the demonstrated adrenocortical hyperplasia is an essential of the menopausal syndromes, for it is well known that the adrenal weight is labile. It is strongly influenced by different infectious conditions, and is possibly dependent on cardiac diseases (von Lucadou 1935—36; Liebegott 1944). It is conceivable that an unintentional selection with regard to such factors might have caused the differences found in the adrenal weight and breadth of the cortex. A special investigation has therefore been made of the material's distribution in respect of acute and chronic infections, and cardiac hypertrophy with and without signs of chronic incompensation. As tables 32 and 33 show, this material shows no such selection with reference to the above sources of error as could by itself explain the larger average adrenal weight in the menopausal syndromes. On the other hand, as the material is too small to allow of statistically significant differences in each separate column in tables 32 and 33, we cannot altogether rule out the possibility that these sources of error may have contributed to the difference in weight found between the menopausal syndromes and the normal cases.

Naturally, it is not out of the question that unintentional selection may have introduced other, not investigated sources of error for the adrenal weight and cortical breadth, such as the vitamin C standard (cf. Hou 1934 and O. Månsson, to be

Table 33. Influence of cardiac hypertrophy and insufficiency on adrenal weight.

Cases of the menopausal syndromes compared with normal women in the menopause with corresponding average age.

Nature of cases	Weight of the adrenal (gm) in cases			
	with cardiac weight ≦ 350 gm	with cardiac weight > 350 gm	with cardiac weight > 300 gm	
			and no cardiac insufficiency	and cardiac insufficiency
Menopausal syndromes 42—93 yrs (includ. 1 man)	8 cases, 16 adrenals 5.78	12 cases, 23 adrenals 6.81	6 cases, 12 adrenals 7.13	8 cases, 15 adrenals 6.59
Normal women in menopause 49—99 yrs	18 cases, 35 adrenals 5.09	11 cases, 22 adrenals 5.78	12 cases, 23 adrenals 5.14	9 cases, 18 adrenals 5.68
Difference	+ 0.69	+ 1.03	+ 1.99	+ 0.91

published), infection of definite bacterial type, and the like, but this must be considered as extremely unlikely.

Hyperplasia of the adrenal cortex is thus typical of the menopausal syndromes. In this respect, then, it resembles the adrenogenital syndrome.

The lipoid content, adenomas, and cancer of the adrenal cortex. No sure deviations from the normal material were observed for the lipoid content of the adrenal cortex in the menopausal syndromes (low lipoid content in 16 of 29, as against 9 of 22 in normal women in the menopause).

Large demarcated cortical adenomas in the adrenals were observed in 6 cases of 41 with menopausal syndromes, that is to say, in about the same frequency as among the normal cases (in 3 of 26 normal women in the menopause; in 4 of 16 normal old men). However, one of the women with marked menopausal syndrome (O. 54/43; 66 years, adiposity of 'buffalo type', suggestions of moon face, large frontal enostoses but no hypertrichosis) showed not only numerous small, partly demarcated cortical adenomas, but also, in the central part of the cortex, a rounded focus about 0.8 mm in diameter on one side, which must probably be taken to be an incipient cancer. That is to say, the focus has no sharp outline, and is built

Table 34. Occurrence of pos. PFR together with the different main symptoms of the menopausal syndromes.

Number of cases with the mentioned symptom	Obesity	Hirsutism	Enostoses	Total
PFR + ...	12	16	11	22
Total	25	32	24	41

up of tightly packed groups of strongly atypical epithelial cells of the most varied appearance: cellular bodies of varying shape and size up to 60×40 µ, different granulation and lipoid content in the cytoplasm, nuclei of varying size up to 35×24 µ, often very polymorphous and with greatly varying chromatin density. Cf. figs. 12 and 13.

The Ponceau-Fuchsin Reaction. This was (weakly) positive in 22 cases with menopausal syndromes, uncertain in 3, and negative in 16. Corresponding figures for normal women in the menopause were 4, 3 and 18. The difference in the frequency of positive PFR is thus 37.7 ± 10.7 %, *i. e.* statistically significant. Vines's supposition (Broster *et al.* 1933, 1938) and the observation of the present author (1942) are hereby confirmed: *Weakly positive PFR is typical of the menopausal syndromes, although not constant.* The tendency to positive PFR in the menopausal syndromes can probably also explain Sudds's finding (1940) of a high frequency of positive PFR in the adrenal cortex of old women. The similarity between adrenal virilism and the menopausal syndromes as regards PFR is obvious. Cf. fig. 21.

Positive PFR proved to be correlated to about the same extent with the different symptoms constituting the menopausal syndromes, *i. e.* obesity of 'buffalo type', hirsutism, and frontal enostoses. This appears from table 34. In the same way, the adrenal hyperplasia occurred in about the same strength together with each of the different main symptoms of the menopausal syndromes. The morphology of the adrenals is therefore insufficient by itself to explain why the menopausal syndromes are composed of different symptoms in different cases.

The distribution of the fuchsinophile granules is of particular interest in two cases of positive PFR. In one, O. 341/43, a 64-year-old woman with strong facial hypertrichosis and slight clitoric hypertrophy (*i. e.* a transitional case to true virilism), the PFR was clearly positive, both in an adenoma as large as a cherry in the cortex of the right adrenal, and in the cortex of the left adrenal. In the second case, the above-mentioned O. 54/43, a 66-year-old woman with enostoses, obesity of 'buffalo type', small adrenocortical adenomas and a suspected incipient cancer focus in one adrenal, the PFR was clearly positive in the adrenal cortex on both sides outside but not inside the adenomas and the cancer. The significance of these findings will be discussed in Chapter VI.

OTHER ENDOCRINE ORGANS

The weights of epiphysis, thyroid and ovary in cases with menopausal syndromes are given in table 35.

Table 35. The weight of epiphysis, thyroid and ovary in the menopausal syndromes compared with that of normal women in the menopause.

Nature of cases	Epiphysis	Thyroid	Ovary
Menopausal syndromes 45—93 yrs	8 cases 0.148(± 0.024) g	9 cases 27.6(± 3.69) g	8 cases, 15 organs 2.85 ± 0.40 g
Women in menopause 49—99 yrs	23 cases 0.150 ± 0.013 g	24 cases 36.5 ± 5.15 g	23 cases, 43 organs 2.25 ± 0.20 g
Difference, $D \pm \varepsilon(D)$	− 0.002(± 0.027) g	−8.9(± 6.33) g	+ 0.60 ± 0.45 g

The epiphysis has normal weight. The thyroid is possibly lighter than normal; the difference from the normal value is nevertheless hardly greater than its standard error. As is seen, the ovaries are not lighter, and are possibly heavier than normally.

The epiphysis was histologically examined in 6 cases with menopausal syndromes, the thyroid in 11, and the ovaries in 19. No material deviations from the normal material could

be found for any of the organs. The man with frontal enostoses (O. 14/44) had histologically normal testes and epididymes.

Histologically, the pancreatic islets were investigated in only 3 cases with concurrent menopausal symptoms and diabetes mellitus. In one of these, O. 183/44, a 71-year-old woman, there was a slight, focal cirrhosis in the pancreas, the islets contained varying quantities of amyloid, and the frequency of the A-cells was probably increased in most of the islets (this is somewhat uncertain, however, due to autodigestion). In the second case, O. 479/43, a 73-year-old woman, the cells in the islets were small, usually with pyknotic or rod-shaped nuclei, and the protoplasm was often vacuolated; there were strikingly many A-cells. In the third case, O. 14/44, the 45-year-old man with enostoses, the frequency of A-cells was similarly strikingly large in most of the islets. Thus, all 3 cases showed changes which are typical of banal pancreatic diabetes (Gellerstedt 1938 b; Ferner 1942; and others). Only in 5 of the cases with menopausal syndromes but without diabetes could anything like satisfactory specimens be prepared according to azan and silver staining methods (Gross-Schultze; cf. Ferner 1942). In 2 of these cases (O. 25/44 and 140/43) the islets were normal, in 3 a very uncertain increase of the number of A-cells was noted (O. 183/44, 192/44 and 193/44). The observations are too few and the results too uncertain to warrant any conclusions whatsoever as to changes in the islets in menopausal syndromes without diabetes.

The parathyroids, finally, were examined macroscopically in 13 cases of menopausal syndromes, and microscopically in 6. No sure deviations from the normal could be noted.

THE CONNECTION OF THE PITUITARY CHANGE WITH THE CLINICAL SYMPTOMS AND THE ADRENOCORTICAL CHANGES IN THE MENOPAUSAL SYNDROMES

As appears from table 36, the picture of the anterior pituitary lobe shows no sure regular variation in the presence of different symptoms belonging to the menopausal syndromes, with

one exception: when there are no enostoses, the frequency of sparsely granulated basophiles seems to be normal, despite the presence of obesity and hirsutism (2 cases) or only hirsutism (1 case). The exception may be accidental, however, and depend on the small number of differentially counted cases without enostoses. That is to say, 4 of the 10 not differentially counted cases with other menopausal symptoms than enostoses showed a relatively large number of sparsely granulated basophiles in the anterior pituitary under the comparison microscope. The even degree of the correlation between pituitary changes and the different main symptoms of the menopausal syndromes furnishes a further similarity with corresponding conditions in the adrenogenital syndrome.

Only the increase of sparsely granulated basophiles, hyaline basophiles and hypertrophic amphophiles in the anterior pituitary, on the one hand, and great frequency of positive PFR and hyperplasia of the adrenal cortex on the other, have been found characteristic of the menopausal syndromes. Furthermore, a correlation can be traced *within* this group, also, between the frequency of the special cells (hyaline basophiles + hypertrophic amphophiles) in the anterior pituitary on the one hand, and the weight of the adrenal on the other. In the 6 cases with at least 0.70 % special pituitary cells, the mean for the adrenal weight was 7.2 gm, in the 8 cases with less than 0.70 % special cells it was 5.8 gm; a division with 0.65 % as dividing-line gave the adrenal weights as 6.8 and 6.0 gm. Needless to say, the groups of cases, as also the differences, are too small for a statistical treatment to yield results, but even so the differences argue for rather than against a positive correlation between the frequency of special cells in the anterior pituitary lobe and the adrenal weight in the group of menopausal syndromes. Thus, in this respect there is a similarity with the normal material, which showed the same tendency towards correlation. On the other hand, there was no correlation between positive PFR in the adrenal cortex and the frequency of special pituitary cells among the menopausal syndromes, for a high frequency of the special cells (more than 0.55 %) occurred in 13 of 19 cases with positive

PFR, and in 13 of 19 with negative or uncertain PFR (in the entire material of differentially counted and estimated cases). In this respect the menopausal syndromes again resemble the adrenogenital cases, where the pituitary change was regular but the positive PFR fairly regular only with virilism.

Summing up the main results, we find that the anterior pituitary in the menopausal syndromes is, in the main, characterised by the same changes as those seen in the adrenogenital syndrome, namely degranulation of the basophile cells and increase of the number of hyaline basophile and hypertrophic amphophiles. The presence of transitional cell types, and the distribution of the cells in the separate hypophyses, indicate that the hypertrophic amphophiles are developed from the basophiles in the menopausal syndromes, also, this taking place partly via the hyaline change.

The parallel between the menopausal syndromes and the adrenogenital syndrome extends further, however; both are typified by hyperplasia of the adrenal cortex, as also by high frequency of positive Ponceau-Fuchsin Reaction, while no regular pathological changes have been demonstrable in other endocrine organs.

5. PROSTATIC HYPERTROPHY

THE HYPOPHYSIS

Weight. The weight of the hypophysis was determined on 20 men with prostatic hypertrophy, aged 56—88 years (mean age 73.3 years); it was 712 $\pm$ 36 mg (mean with standard error). In 35 men aged 50—81 years (mean age 63.1 years) the hypophysis weighed 741 $\pm$ 20 mg, and in 16 men aged 66—81 years (mean age 70.5 years) it weighed 769 $\pm$ 28 mg. Thus, there were no probable differences in weight.

Cell frequencies of the anterior pituitary lobe. Table 37 shows the results from the differential count of the anterior pituitaries in 12 cases with prostatic hypertrophy, with mean age 72.8 years. For comparison, the table includes correspond-

Table 36. Correlation between the frequency of anterior pituitary cells and the main symptoms of the menopausal syndromes.

Symptoms		No of cases	Frequency of ant. pit. cells in %, mean			
			1. Sparsely gran. basoph.	2. Hyaline basoph.	3. Hypertrophic amphoph.	4. Total 2. + 3.
Obesity	present	11	8.1	0.16	0.48	0.64
	not present	7	9.1	0.18	0.52	0.69
Hirsutism	present	11	7.2	0.11	0.53	0.64
	not present	7	10.4	0.26	0.43	0.69
Enostoses	present	15	9.0	0.16	0.52	0.68
	not present	3	5.7	0.19	0.37	0.55
Cardiac hypertrophy	present	12	8.2	0.15	0.49	0.64
	not present	6	9.0	0.21	0.50	0.71

ing means of 12 normal men over 50 years, with mean age 64.2 years. The standard errors of the differences in table 37 have been calculated according to usual methods. As the compared groups only comprise 12 cases each, these errors are unreliable. However, the uncertainty which ordinary statistical methods involve by reason of *the small number* of the observations in *each group separately* can be considerably reduced according to a method suggested by G. Dahlberg (cf. Key 1932). Following this method, one first determines the σ_c common to the two groups that are to be compared, according to the formula

$$\sigma_c^2 = \frac{1}{n_1 + n_2 - 2} \cdot [\Sigma (M_1 - d_1)^2 + \Sigma (M_2 - d_2)^2],$$

where n_1 and n_2 are the number of observations in the different groups, M_1 and M_2 the means of the different groups, and d_1 and d_2 the deviations of the separate values from the mean in the respective groups. The standard error of the difference $M_1 - M_2$ then has the form

$$\varepsilon (D) = \pm \sigma_c \cdot \sqrt{\frac{1}{n_1} + \frac{1}{n_2}}.$$

Table 37. Frequency of different cell types in the anterior pituitary of men with prostatic hypertrophy.

For comparison, corresponding values of normal men over 50 years old.

Case No.	Age in years	Frequency of different cell types in %									
		1. Acidophiles	2. Normal basophiles	3. Sparsely granul. basophiles	4. Total 2. + 3.	5. Chromophobes with small nuclei	6. Chromophobes with large nuclei	7. Total 5. + 6.	8. Hyaline basophiles	9. Hypertrophic amphophiles	10. Total 8. + 9.
$^{456}/_{42}$	51	30	10	10	20	38	11	49	0.06	0.53	0.59
$^{20}/_{44}$	56	26	10	9.2	20	41	13	54	0.12	0.91	1.03
$^{476}/_{44}$ [1]	57	24	9.5	6.5	16	48	12	59	0.01	0.63	0.64
$^{458}/_{44}$	70	26	7.8	4.9	13	48	12	61	0.19	0.61	0.80
$^{477}/_{44}$	70	39	8.9	6.1	15	36	9.1	45	0.06	0.52	0.58
$^{453}/_{42}$ [2]	76	23	12	7.6	20	52	5.3	57	0.08	0.19	0.27
$^{426}/_{44}$ [1]	77	32	5.4	8.6	14	45	8.5	53	0.10	0.63	0.73
$^{481}/_{43}$	78	33	6.3	5.7	12	50	4.9	55	0.06	0.15	0.22
$^{130}/_{44}$ [3]	78	40	7.8	3.4	11	45	2.8	48	0.72	0.07	0.80
$^{95}/_{44}$	86	33	16	6.1	22	41	3.9	44	0.22	0.21	0.43
$^{12}/_{44}$	87	34	7.7	4.9	13	42	10	53	0.11	0.84	0.95
$^{477}/_{43}$	88	31	4.5	5.1	9.6	52	6.7	59	0.03	0.69	0.72
Prostatic hypertrophy Mean of 12: 72.8 yrs		30 9 ± 1.57	8.8 ± 0.89	6.5 ± 0.56	15.5 ± 1.19	44.8 ± 1.54	8.3 ± 1.00	53.1 ± 1.61	0.15 — 0.055	0.50 ± 0.080	0.65 ± 0.072
Normal men Mean of 12: 64.2 yrs		31.7 ± 1.74	12.2 ± 1.86	4.5 ± 0.58	16.6 ± 1.90	46.1 ± 1.40	5.2 ± 0.41	51.3 ± 1.58	0.05 ± 0.025	0.30 ± 0.029	0.35 ± 0.030
Difference $D \pm \varepsilon(D)$		− 0.8 ± 2.34	− 3.4 ± 2.06	+ 2.0 ± 0.81	− 1.1 ± 2.24	− 1.3 ± 2.08	+ 3.1 ± 1.08	+ 1.8 ± 2.26	+ 0.10 ± 0.060	+ 0.20 ± 0.085	+ **0.30** ± **0.078**

[1] Also diabetes mell.

[2] Chromophobe adenoma in the ant. pit., 2.1 × 4.2 mm.

[3] Hyaline basophiles in the post. lobe too.

A calculation according to this method gave the same values for the standard errors of the differences as those recorded in table 37, with the exception that $\varepsilon(D)$ in column 10 was somewhat smaller (0.077). In other words, table 37 shows a statistically significant increase of the number of special cells (hyaline basophiles + hypertrophic amphophiles; the difference is nearly 4 times its standard error), a probable increase of sparsely

granulated basophiles (difference about 2.5 times its standard error), and a probable increase of chromophobes with large nuclei (difference nearly 2.9 times its standard error) in men with prostatic hypertrophy as compared with normal men, *i. e.* the same change as that found in the menopausal syndromes. The observed differences could not be due to the difference in age between the groups in table 37: a comparison with younger men shows that the lower mean age in the control group in table 37 should rather have decreased the differences in cell frequencies (cf. table 14). The increase of the special cells in the anterior pituitary is further confirmed when the differentially counted material in table 37 is combined with the cases of prostatic hypertrophy, where the frequency of the special cells was only estimated (table 38).

Table 38. Occurrence of the special cells in the anterior pituitary of men with prostatic hypertrophy compared with that of normal men over 50 years old.

Combined material of hypophyses differentially counted and examined under the comparison microscope. Cf. tab. 15.

Nature of cases	Age in years, mean	Total number of examined cases	Frequency of the special cells		
			Number of cases with > 0.55 %	Number of doubtful cases	Number of cases with < 0.55 %
Prostatic hypertrophy 51—88 years	73.7	15	10 66.7 %	1 6.7 %	4 26.7 %
Normal men 50—84 years	65.1	16	1 6.3 %	0	15 93.8 %
Difference, $D \pm \varepsilon(D)$ in %	—	—	+ 60.4 ± 13.6	+ 6.7	− 67.1 ± 12.9

Objections with regard to the exceptions, which do not show the pituitary picture typical of the prostatic hypertrophy group in its entirety, doubtless have as little force in prostatic hypertrophy as in the menopausal syndromes (cf. p. 120). *Thus, the anterior pituitary lobe of men with prostatic hypertrophy is characterised with certainty by increase of the number of special cells (hyaline basophiles and hypertrophic amphophiles), and*

Table 39. Basophile invasion and colloid content in the hypophyses of men with prostatic hypertrophy compared with those of normal men over 50 years. — Cf. table 17.

Nature of cases	Age in years, mean	Total number of examined cases	Basophile invasion of neurohypophysis			Colloid content		
			slight	moderate	strong	slight	moderate	strong
Prostatic hypertrophy 51—88 years	72.8	12	5 41.7 %	1 8.3 %	6 50.0 %	2 16.7 %	6 50.0 %	4 33.3 %
Normal men 50—84 years	62.9	14	6 42.9 %	3 21.4 %	5 35.7 %	5 35.7 %	7 50.0 %	2 14.3 %
Difference, $D \pm \varepsilon(D)$ in %	—	—	-1.2 ± 19.4	-13.1 ± 13.6	$+14.3 \pm 19.3$	-19.0 ± 16.7	$\pm 0 \pm 19.7$	$+19.0 \pm 16.5$

probably by degranulation of basophiles (and increased frequency of chromophobes with large nuclei), *i. e. the same change as that seen in the menopausal syndromes — and at the same time the same change, though less pronounced quantitatively, as that in the adrenogenital syndrome.* Unlike the menopausal syndrome cases, however, the men with prostatic hypertrophy showed no increase of the total number of basophiles in the hypophysis. Figs. 8, 10 and 11 illustrate the change observed in such men.

Observations concerning the structure of the hypophysis, by the side of the differential count. Adenomas (1 chromophobe) were observed in the anterior lobe of one of the 15 men with prostatic hypertrophy, as against 4 of 72 cases among the normal cases (adult men and women). — Small acidophiles were observed in 2 of 12 men with prostatic hypertrophy, and in 2 of 12 normal old men. — Table 39 shows the occurrence of basophile invasion in the neural lobe and of colloid in the anterior lobe (including the boundary region to the neural lobe) in men with prostatic hypertrophy. No differences from the normal material could be made probable. — Hyaline basophiles among the cells invading the posterior lobe were found in one man with prostatic hypertrophy, also (O. 130/44).

The origin of the hypertrophic amphophiles. Transitional cell forms between basophiles (sparsely granulated and hyaline) and hypertrophic amphophiles were observed as regularly among men with prostatic hypertrophy as in the groups discussed earlier on. The men with prostatic hypertrophy also showed the hypertrophic amphophiles to be accumulated in the basophile regions (in 11 cases of 12), and as a rule together with the hyaline basophiles. *In this group too, then, it can be assumed that the hypertrophic amphophiles are in large measure developed from the basophiles, probably in part via the hyaline change.*

THE ADRENALS

Weight and cortical breadth. The weight of the adrenals was determined in 20 men (39 organs) with prostatic hypertrophy aged 56—86 years, with mean age 72.3 years. The mean weight was 5.85 ± 0.24 gm. In 17 normal men (33 organs) aged 64—81 years, with mean age 70.3 years, the mean weight was 4.99 ± 0.33 gm. The difference is thus $+ 0.86 \pm 0.41$ gm, *i.e.* about 2.1 times its standard error. The probability that the difference is not conditioned by chance is consequently greater than 96: 100. Nor should the difference be due to an unintentional selection with reference to infection or cardiac diseases, as tables 40 and 41 show.

Table 40. Influence of infection on adrenal weight.

Men with prostatic hypertrophy compared with normal men of corresponding average age. — Cf. tab. 32.

Nature of cases	Weight of the adrenal (gm) in cases		
	without infection	with acute infection	with chron. infection
Prostatic hypertrophy 56—88 yrs	12 cases, 24 adrenals 5.87	7 cases, 13 adrenals 5.92	1 case, 2 adrenals 5.10
Normal men 64—81 yrs	7 cases, 14 adrenals 4.51	9 cases, 17 adrenals 5.49	1 case, 2 adrenals 3.95
Difference	+ 1.36	+ 0.43	+ 1.15

Table 41. Influence of cardiac hypertrophy and insufficiency on adrenal weight.

Men with prostatic hypertrophy compared with normal men of corresponding average age.

Nature of cases	Weight of the adrenal (gm) in cases			
	with cardiac weight ≦ 450 gm	with cardiac weight > 450 gm	with cardiac weight > 350 gm	
			and no cardiac insuffic.	and cardiac insuffic.
Prostatic hypertrophy 56—88 yrs	9 cases, 17 adrenals 6.28	11 cases, 22 adrenals 5.51	5 cases, 9 adrenals 5.78	11 cases, 22 adrenals 5.89
Normal men 64—81 yrs	9 cases, 17 adrenals 5.47	8 cases, 16 adrenals 4.46	8 cases, 16 adrenals 5.71	6 cases, 12 adrenals 4.14
Difference	+ 0.81	+ 1.05	+ 0.07	+ 1.75

The breadth of the adrenal cortex was determined in 12 men with prostatic hypertrophy, and in 14 normal men over 50 years of age; it was 1.41 (± 0.12) and 1.21 (± 0.062) mm. The difference of + 0.20 (± 0.14) mm is thus not probable.

Consequently, it is doubtful whether an adrenocortical hyperplasia is characteristic of men with prostatic hypertrophy. The material is too small for this question to be decided with anything like certainty. However, as will be shown in Chapter VI, this does not materially affect the main question, *i. e.* that of the genetic importance of the pituitary change in prostatic hypertrophy and in the menopausal and the adrenogenital syndromes. The important thing is that, besides the pituitary change — which is statistically significant — there is a certain probability of adrenocortical hyperplasia in men with prostatic hypertrophy also.

The lipoid content and adenomas of the adrenal cortex. No deviations from the normal material were shown by the lipoid content of the cortex in men with prostatic hypertrophy (low lipoid content in 4 of 12 cases, against 5 of 13 normal cases). Large demarcated adrenocortical adenomas were not

found in any case of 16 men with prostatic hypertrophy, but were found in 4 of 16 normal old men. Plainly, the difference may be due to chance.

The ponceau-fuchsin reaction. This was (weakly) positive in 5, uncertain in 3, and negative in 5 men with prostatic hypertrophy. Corresponding figures for normal men over the age of 50 years were 5, 2 and 8 — *i. e.* no differences. On the other hand, it would not be justifiable to talk of a difference between menopausal syndromes and men with prostatic hypertrophy as regards positive PFR (difference: 15.2 ± 15.6 %). Cf. fig. 22.

OTHER ENDOCRINE ORGANS

The various weights are shown in table 42. The investigated groups are admittedly small, but it should be possible to deduce from the results that large deviations in the weight of epiphysis, thyroid or testes do not mark off men with prostatic hypertrophy from the normal cases.

Table 42. The weight of epiphysis, thyroid and testis of men with prostatic hypertrophy compared with that of normal men of corresponding age.

Nature of cases	Epiphysis	Thyroid	Testis
Prostatic hypertrophy 56—88 yrs	11 cases 0.163(± 0.028) g	19 cases 28.6 ± 4.14 g	18 cases, 36 organs 15.2 ± 0.87 g
Normal men 50—84 yrs	26 cases 0.142 ± 0.015 g	30 cases 31.1 ± 2.95 g	28 cases, 56 organs 15.3 ± 0.80 g
Difference, $D \pm \varepsilon(D)$	+ 0.021(± 0.032) g	−2.5 ± 5.09 g	− 0.1 ± 1.18 g

A histological examination was made of the epiphysis in 6 cases of the men with prostatic hypertrophy, of the thyroid in 8 and of the testes in 11. No great differences from the normal were observed. Owing to autodigestion, no definite pronouncement can be made on the pancreatic islets in the two cases with prostatic hypertrophy and diabetes. The fre-

quency of the A-cells of the islets may possibly have been increased in one of them (O. 426/44). In a further 7 men with prostatic hypertrophy the islets were examined histologically: 4 cases were normal, 1 showed relative increase of the A-cells, 1 patches of hyalinisation, and 1 was indeterminable on account of autodigestion. The parathyroids were investigated, macroscopically only, in 19 men with prostatic hypertrophy, and proved normal.

Summing up the main results, we find that the anterior pituitary lobe in men with prostatic hypertrophy is, in the main, characterised by the same changes as those seen in the menopausal syndromes — and at the same time, the same changes as those in the adrenogenital syndrome, although less pronounced; that is to say, an increase of the number of special cells (hyaline basophiles and hypertrophic amphophiles) and a probable increase of the number of sparsely granulated basophiles and chromophobes with large nuclei. In men with prostatic hypertrophy, too, the hypertrophic amphophiles probably develop from the basophiles, possibly with the hyaline basophiles as intermediate phase.

A certain — quite faint — probability that adrenocortical hyperplasia is a characteristic of men with prostatic hypertrophy has also emerged. The Ponceau-Fuchsin Reaction is not infrequently weakly positive in men, whether they have prostatic hypertrophy or not, and no difference between the groups has been demonstrable. The other endocrine organs have not shown any regular pathological changes in men with prostatic hypertrophy.

6. DIABETES MELLITUS, HYPERPARATHYROIDISM, EUNUCHOIDISM AND ADDISON'S DISEASE

This group of cases has been compiled in order to illustrate the specificity of the pituitary change demonstrated in the adrenogenital syndrome, the menopausal syndromes and prostatic hypertrophy. Assuming these three diseases are all characterised by an adrenocortical hyperfunction, the question

then is whether other endocrine disturbances with certain symptoms in common with the above three, but with no signs of adrenocortical hyperfunction, also lack the demonstrated pituitary change.

On this conception, it is natural to choose cases of diabetes mellitus for investigation, for certain authors have assumed diabetes is characteristic of the menopausal syndromes (see survey of the literature). Cases with parathyroid hyperfunction have been investigated for the same reason. Eunuchoidism, on the other hand, has been chosen on account of the possibility of gonadal failure's setting up the adrenogenital syndrome, that is to say, on account of a possible genetic similarity with the adrenogenital syndrome (cf. survey of the literature). Addison's disease, finally, is interesting as a clinical contrast to the adrenogenital syndrome.

DIABETES MELLITUS

The group contains 6 cases, 5 of them with differential count of the hypophysis.

Case reports:

O. 51/44. 49-year-old man. Slight diabetes for 8 years. Treated during the last few years only by diet. Died from facial phlegmone and sepsis. Of medium height, normal flesh, normal calvaria, normal prostate. Hypophysis 905 mg, macroscopically normal, differentially counted. Perceptible increase of the number of A-cells of the pancreatic islets. Other endocrine organs normal. — *O. 429/40.* 56-year-old woman. Previously had gastric trouble. Thirst, polyuria, tiredness and loss of weight for 2 months. Died from coma diabeticum. Of medium height, normal flesh, calvaria and growths of hair normal. Anterior pituitary histologically normal; no increase in the number of hyaline basophiles or hypertrophic amphophiles (examined with comparison microscope). Pronounced post-hydropic degeneration of the pancreatic islets. — *O. 157/44.* 59-year-old woman. Diabetes for 1 year. Died from acute appendicitis and peritonitis. Of medium height, fat, calvaria and growths of hair normal. Hypophysis 786 mg, macroscopically normal, differentially counted. Strong amyloidosis of the pancreatic islets; numerous A-cells in some of the islets. Nodous colloid goitre without histological signs of hyperfunction. Other endocrine organs normal. — *O. 21/44.* 60-year-old man. Fat for 20 years. Diabetes for 12 years, with insulin treatment during the last 2. 2 years before death he had cancer labii, successfully treated with radium. Died from ruptured arteriosclerotic aorta aneurysm

(+ phlegmone in the right hand). Rather over medium height, great obesity, calvaria and prostate normal. Hypophysis 716 mg, macroscopically normal, differentially counted. Pancreas not preserved. Remarkably broad adrenal cortex: 1.6 mm; PFR uncertain. Other endocrine organs normal. — *O. 141/43.* 63-year-old woman. Symptoms of diabetes for 6 weeks. Died from granulocytopenia + embolia pulm. Short, proportional obesity (not 'buffalo type'), calvaria and growths of hair normal. Hypophysis macroscopically normal, differentially counted. Most of the pancreatic islets very rich in A-cells. Other endocrine organs normal (the epiphysis not investigated, however). — *O. 36/44.* 72-year-old man. Symptoms of diabetes for 1 year. Died from cerebral infarct (+ lung oedema). Of medium height, thin, normal calvaria and prostate. Hypophysis 698 mg, macroscopically normal, differentially counted. Great increase of the number of A-cells in most of the pancreatic islands, often more than 50 %. Colloid struma without signs of hyperfunction. Other endocrine organs normal.

The anterior pituitary. The results of the differential count are given in table 43. As can be seen, there is fairly good agreement between the means of the 5 cases with diabetes

Table 43. Frequency of different cell types in the anterior pituitary of cases with diabetes mellitus compared with that of normal men and women with corresponding average age.

Case No.	Age in years	Sex	Frequency of different cell types in %									
			1. Acidophiles	2. Normal basophiles	3. Sparsely granul. basophiles	4. Total 2. + 3.	5. Chromophobes with small nuclei	6. Chromophobes with large nuclei	7. Total 5. + 6.	8. Hyaline basophiles	9. Hypertrophic amphophiles	10. Total 8. + 9.
$^{51}/_{44}$	49	♂	35	4.2	2.3	6.6	53	5.6	59	0.00	0.31	0.31
$^{157}/_{44}$	59	♀	27	6.0	5.4	11	56	5.9	62	0 03	0.23	0.26
$^{21}/_{44}$	60	♂	39	6.7	5.7	12	40	7.1	48	0.09	0.93	1.03
$^{141}/_{43}$	63	♀	25	12	2.3	14	58	3.1	61	0.01	0.17	0.18
$^{36}/_{44}$	72	♂	32	13	6.4	19	42	7.2	49	0.00	0.37	0.37
Diabetes 5 cases	60.6	3 ♂ + 2 ♀	31.6	8.4	4.4	12.6	49.8	5.8	55.8	0.03	0.41	0.43
Normal 27 cases	66.4	12 ♂ + 15 ♀	31.3	10.1	5.2	15.2	46.1	6.9	53.1	0.05	0.30	0.34

and those of 27 endocrinely normal old men and women. In this respect the results tally with those of Hawking (1936). — Only in one diabetic were there remarkably high values for hyaline basophiles and hypertrophic amphophiles (O. 21/44, 60-year-old man, normal prostate, pancreas not preserved). This case is also characterised by great obesity and a remarkably broad adrenal cortex. It is therefore possible that an adrenocortical hyperfunction marks off this case of diabetes from the remaining 4 in the group, who show no plain menopausal symptoms, prostatic hypertrophy or adrenocortical hyperplasia, and in whom the pancreatic islets showed the changes typical of banal 'pancreatic diabetes'. The same held for the 6th case (O. 429/40), whose anterior pituitary showed few hyaline basophiles and hypertrophic amphophiles under the comparison microscope. It is true that the material is small, but it nevertheless shows that cases of diabetes mellitus without menopausal symptoms, prostatic hypertrophy or adrenocortical hyperplasia are not as a rule characterised by the pituitary change typical of the adrenogenital syndrome.

HYPERPARATHYROIDISM

A differential count has been made of the hypophyses of 2 pronounced cases.

The first case (O. 420/41), a 51-year-old woman with acute fatal hyperparathyroidism, has been fully described by the present author in 1943. She was somewhat thin, growths of hair and calvaria normal; adrenals macroscopically normal, the cortex fairly broad. — The anterior pituitary macroscopically normal. Microscopic examination revealed a strikingly large number of chromophobes with large nuclei — though smaller and more compact than those of the hypertrophic amphophiles — and very large or even enormous cellular body with foamy or extremely finely granulated protoplasm. As there was also an abundance of sparsely granulated basophiles and of transitional forms between these and the above-mentioned chromophobes, these large chromophobes were called 'degranulated basophiles according to Kraus'; the significance of the change was not discussed (Mellgren 1943). A later differential count (where the large chromophobes were registered as 'chromophobes with large nuclei' in accordance with the division in this thesis) yielded the values for the cell frequencies, which do not differ from the normal values; hyaline basophiles + hypertrophic amphophiles 0.33 % (one horizontal section).

The second case of hyperparathyroidism (O. 164/43) was a 46-year-old woman with nephrocirrhosis glomerulonephritica and cardiac hypertrophia, who died from uraemia. She was short, thin, with normal growths of hair and thin calvaria. The parathyroids were all appreciably hyperplastic, total weight 1.26 gm; the microscope showed them composed of water-clear cells and chief cells in a dense mosaic, with pseudoglandular arrangement in places, free from interstitial fat and poor in intracellular fat granules. Very pronounced general osteoporosis. Calcium precipitations in the renal parenchyma. Adrenals slightly enlarged, the cortex about 1.5 mm. Other endocrine organs normal. Without doubt a typical case of secondary hyperparathyroidism due to chronic renal insufficiency (cf. Castleman and Mallory 1935, 1937). — The hypophysis was macroscopically normal. The anterior pituitary was characterised by the same histological picture as in the case described above, *i. e.* a large number of chromophobes with very large cellular bodies but only moderately large and relatively dense nuclei (cf. figs. 14 and 15). The frequency of hyaline basophiles + hypertrophic amphophiles was only 0.46 % (3 sagittal sections).

Hyperparathyroidism (without the main symptoms of the adrenogenital syndrome at the same time) is thus not characterised by the pituitary picture typical of the adrenogenital syndrome. On the other hand it is likely that the chromophobes with very large cellular body (degranulated basophiles according to Kraus?) are typical of the anterior pituitary in hyperparathyroidism. This conception was advanced by Å. Wilton (lecture to the *Svenska Patologförening* 1944, to be published), who observed identical pituitary changes in a still more pronounced form in another case of hyperparathyroidism. The significance of the pituitary change in hyperparathyroidism will be passed over here; it is outside the scope of this thesis.

EUNUCHOIDISM

Two cases of eunuchoidism have been investigated (without differential count of the hypophysis).

The first (O. 30/38), a 55-year-old man with typical stature, enormous obesity, high voice, no beard, feminine pubes and atrophic genitals (testes, prostate, seminal vesicles, penis), has been fully described by the present author in 1942. His skull was thick with smooth internal osseous deposits on the anterior lateral parts. The germinal tissue of the testes was highly atrophic, there was no spermiogenesis, the interstices were broad, in part fibrotic and in part the seat of great hyperplasia of the interstitial cells.

The adrenals were normal except for a cortical adenoma the size of a cherry on one side, and clearly (weakly) positive PFR in the cortex on both sides. The anterior pituitary: Acidophiles normal in number, often small. Plentiful basophiles, especially the sparsely granulated type. Very numerous typical hypertrophic amphophiles and a moderate number of hyaline basophiles, most of them nevertheless atypical by reason of diffuse cellular outlines and quite small hyaline fields. In addition, subsequent inspection showed a small number of 'castration cells' of the kind described in the following case.

The second case (O. 220/42) — which might also be entitled Syndroma Morgagni + eunuchoidism — was a 57-year-old man with unknown anamnesis. He died suddenly from myocarditis chronica. Heavily built, obesity of 'buffalo type', feminine features, downy hair on upper lip and chin, feminine pubes, typical frontal enostoses and osteoporosis (ribs investigated). Testes the size of peas, consisting microscopically of connective tissue calcified in parts with atrophic tubular remains. Epididymes small and fibrotic, prostate the size of a thumb's end, penis as large as a thumb. Adrenals rather larger than normal, with broad cortex and a cortical adenoma the size of a cherry on one side; PFR negative. Other endocrine organs macroscopically normal. The anterior pituitary: Acidophiles normal in number, to a large extent quite small. Few normal and sparsely granulated basophiles. Very many typical hypertrophic amphophiles, relatively few hyaline basophiles. On the other hand, very many pale basophiles of peculiar appearance: large cellular body, nucleus resembling that of a normal basophile or smaller and denser, and — as a special characteristic — a large circular 'vacuole', reminiscent of a hypertrophic Golgi zone (cf. figs. 16 and 17); the protoplasm palely basophile (to chromophobe), often with several small vacuoles and for the most part recalling colloid or clumped granules. A few transitional forms to normal basophiles, *i. e.* cells of the appearance described, together with distinct basophile granules in the protoplasm.

It can be left open whether the above peculiar cells are identical with any of the many pathological types of pituitary cell described in eunuchoidism by earlier authors (cf. survey by Romeis 1940). It may also be left open whether the cells described correspond to the castration cells in animals, which they undeniably greatly resemble. The only relevant factor here is that the above-mentioned 'castration cells' are foreign to the pituitary picture in the adrenogenital syndrome (menopausal syndromes and prostatic hypertrophy).

The pituitary change in the two investigated cases of eunuchoidism is thus composed *both* of the change typical of the adrenogenital syndrome (increase of the number of hyper-

trophic amphophiles and hyaline basophiles) *and* of changes foreign to the adrenogenital syndrome ('castration cells'). One of the two men with eunuchoidism (O. 220/42) unquestionably showed the main symptoms characteristic of Syndroma Morgagni (obesity of 'buffalo type' and frontal enostoses), together with slight adrenocortical hyperplasia. In this case, then, there were the same criteria for the probability of adrenocortical hyperfunction as in the menopausal syndromes generally. In the second case (O. 30/38) there were no certain criteria for an adrenocortical hyperfunction, but it seems not unlikely that the great obesity, the adrenocortical adenoma and the positive PFR are signs of such an one. It is therefore possible that the same parallel between pituitary change (increased frequency of hyaline basophiles and hypertrophic amphophiles) and adrenocortical hyperfunction obtains in the two cases with eunuchoidism as in the adrenogenital and the menopausal syndromes (cf. below, Chapter VI).

It is highly unlikely that the strong destruction of the testes which characterised the second eunuchoidism case (O. 220/42) resulted from disturbances in other endocrine organs; it was probably the result of a local process. It is therefore likely that gonadal failure may induce 'Cushingoid habitus' and Syndroma Morgagni. One cannot go much further than a supposition, however, since the origin of the testicular change is not known for certain in either of the eunuchoidism cases. The same applies to the 'castration cells' in the hypophysis. However, it is conceivable that these cells arise as a reaction to the destruction of the interstitial testicular cells, since the pituitary cells in question were plentiful in the second case of eunuchoidism, but few in the first.

ADDISON'S DISEASE

A differential count of the hypophysis has been made in two pronounced cases of Addison's disease.

The first (O. 187/43) was a 26-year-old woman. She had previously had no subjective disease symptoms. For 2 months there had been increasing tiredness, vomiting, abdominal pains, thirst, irregular menses, falling blood

pressure (95/55—75/50), low blood sugar and, finally, typical pigmentation (though not in the oral cavity). Died during increasing hypotonia, despite DOCA. Autopsy findings: Medium height, normal habitus; flesh, calvaria, hair growths and external genitals normal. Obsolete pulmonary tuberculosis with caverns and fresh foci, and intestinal tuberculosis. Almost complete acute caseous destruction of both adrenals by tuberculosis; the small cortical remains were poor in lipoid and showed negative PFR. Other endocrine organs normal on the whole.

Hypophysis 788 mg, macroscopically normal. Results of the differential count of the anterior lobe: Acidophiles 22, normal basophiles 0.9, sparsely granulated basophiles 5.4, chromophobes with small nuclei 53, chromophobes with large nuclei 18, hyaline basophiles 0.06 and hypertrophic amphophiles 0.63 %. Most of the sparsely granulated basophiles characterised by indistinctly outlined, often clumped granules and diffuse cell contours.

The second case (O. 416/37) was a 37-year-old woman. 5 children. Previously healthy. For 7 years she had had periods of amenorrhoea, interrupted by irregular uterine bleedings. Gastric trouble for 2 years: achylia gastrica. During a few months she had increasing tiredness, falling blood pressure (105/80—60/30) and typical pigmentation. Died from bronchopneumonia. Autopsy findings: Medium height, normal habitus, rather thin, normal calvaria. Persistent thymus, large as a child's hand. Diffuse colloid struma. Ovaries as large as chestnuts, fibrotic, with some simple cysts. Adrenals atrophic; the cortex as thin as paper, almost entirely destroyed by typical, non-specific inflammatory atrophy.

Hypophysis macroscopically normal. Results of the differential count of the anterior lobe (made on a horizontal section): Acidophiles 17, normal basophiles 2.5, sparsely granulated basophiles 8.9, chromophobes with small nuclei 54, chromophobes with large nuclei 17, hyaline basophiles 0 and hypertrophic amphophiles 0.50 %. The basophiles showed the same changes as in the first case.

The observed decrease of the normal basophiles and the appearance of sparsely granulated basophiles with clumped granules and diffuse cell contours (decomposition forms according to Kraus) in the anterior pituitary in Addison's disease tally with observations by several earlier investigators (Kraus 1923, 1927; Crooke and Russel 1935; Hawking 1936; Berblinger 1942). Hyaline basophiles and hypertrophic amphophiles have not previously been described in this disease.

As Berblinger and others have shown, the non-specific inflammatory atrophy of the adrenals in Addison's disease must, like the tubercular destruction, be expected to be primary to the cited change of the pituitary basophile cells (Berblinger

1942). One of these observed cases of Addison's disease showed a slight but certain increase in the number of hyaline basophiles and hypertrophic amphophiles, but the other did not; here, however, the same consequences to the hypophysis of deficient adrenal function must be allowed for. Thus, slight signs of the pituitary change characterising the adrenogenital syndrome, *i. e.* cases with adrenocortical hyperfunction, may occur in the human anterior pituitary as a result of adrenal destruction, also. This, however, was not so in the second of the present author's cases. On the other hand, degranulation and 'decomposition' of the basophiles, with clumping of basophile granules, seems to be a constant result of adrenocortical destruction in man — that is to say, a pituitary change which has certain resemblances to the one in adrenocortical hyperfunction, but is not identical with it. For the present, a definite conclusion as to the significance of these findings can hardly be drawn. However, they do not confute the view that destruction of the adrenals (together with other influences on the pituitary?) may set up a raised — compensatory — corticotropic pituitary function or, in other words, that signs of raised corticotropic function is common to the pituitary picture in the adrenogenital syndrome and that in Addison's disease. This conception agrees well with the above-cited experiments on animals by Severinghaus, Ingle and Kendall (cf. Chapter II).

Summing up, it is found that the anterior pituitary in diabetes without the main symptoms of the adrenogenital syndrome is also not characterised by the histological change typical of the adrenogenital syndrome, either. In hyperparathyroidism, the anterior pituitary is probably characterised by chromophobes with moderately large, dense nuclei and very large cellular body, but not by hyaline basophiles or hypertrophic amphophiles. Of the two investigated cases of eunuchoidism, one also showed Syndroma Morgagni, the other enormous obesity, adrenocortical adenoma and positive Ponceau-Fuchsin Reaction in the adrenal cortex; in addition to cells resembling the castration cells of rodents, both hypophyses showed the change typical of the adrenogenital syndrome

(hyaline basophiles and hypertrophic amphophiles). The correlation between the latter pituitary change on the one hand, and clinical symptoms of the adrenogenital syndrome with adrenocortical changes (hyperplasia and positive PFR) on the other, should consequently remain unbroken. It is furthermore likely that gonadal failure may induce 'Cushingoid habitus' and Syndroma Morgagni. — In Addison's disease, finally, the human anterior pituitary lobe presents a picture which resembles but is not identical with that in the adrenogenital syndrome. However, one of the two investigated cases of Addison's disease showed an increase of hyaline basophiles and hypertrophic amphophiles in the anterior pituitary. It is conceivable that, in this case also, the pituitary change in point corresponds to a corticotropic function set up — by way of compensation — through the destruction of the adrenal cortex.

CHAPTER VI

DISCUSSION

It was known earlier on that, in Cushing's syndrome, the anterior pituitary is characterised by an abundance of hyaline basophiles (Crooke's cells), and that in a number of such cases it also shows numerous hypertrophic amphophiles. On the other hand, no definitely regular anterior pituitary changes have hitherto been reported from adrenal virilism although, like Cushing's syndrome, this condition is typified by adrenocortical hyperfunction. Nor has any regular pituitary change been established in 'Cushingoid habitus' or Syndroma Morgagni (here grouped under the designation of 'the menopausal syndromes'), which have been suspected of being mild forms of Cushing's disease. Finally, there are no data as to regular pituitary change in prostatic hypertrophy, which, on a theory of the present author, is possibly also distinguished by hyperfunction of the adrenal cortex (see above, Chapter II).

The main results from this thesis are that the anterior pituitary shows, on the whole, the same histological change in Cushing's syndrome, adrenal virilism, the menopausal syndromes and prostatic hypertrophy, namely, increase of the number of special cells (hyaline basophiles + hypertrophic amphophiles), together with a less constant increase of the number of sparsely granulated basophiles. The only difference between the above groups is that the pituitary change is quantitatively far stronger in Cushing's disease and adrenal virilism than in the menopausal syndromes and prostatic hypertrophy.

The functional significance of the pituitary change from a cytological viewpoint. As far as it can be judged

purely on the morphology of the pituitary cells, the question of the functional significance of the observed pituitary change is primarily concerned with the origin of the hypertrophic amphophiles. This investigation was able to show that, for each separate group in point — as also in normal adults — the hypertrophic amphophiles were in all probability developed wholly or in part from basophiles, to some extent at least with hyaline basophiles as intermediate phase. This conclusion is based partly on the regular occurrence of transitional cells (previously also observed by Gellerstedt in Cushing's syndrome, 1939), and partly on the distribution of the cells within the individual hypophyses. Another observation pointing the same way is that the adrenogenital syndrome — where these special cells are most numerous — is accompanied by an increase in frequency of the hypertrophic amphophiles at the expense of the hyaline basophiles, with the duration of the disease. This is further borne out by the fact that the hypertrophic amphophiles usually predominate in the menopausal syndromes and in prostatic hypertrophy, which, compared with the adrenal syndrome, are lengthy and mild diseases.

The present author is in full agreement with the conclusions of earlier investigators that the structure of the hyaline basophiles (Crooke 1935; Gellerstedt 1938 a, 1939) and the hypertrophic amphophiles (Gellerstedt 1939) indicate an enhanced function, especially in view of the experimental observations and observations touching other endocrine organs which have been cited above (cf. survey of the literature, in particular pp. 16—19). — As Berblinger has shown (1943; cf. above p. 17) that the basophile granules of the human anterior pituitary are bearers of the corticotropic factor, it is not unlikely that the anterior pituitary change observed here implies corticotropic hyperfunction.

The hypophysis and adrenal cortex in the adrenogenital and the menopausal syndromes. In Chapter V, the observation has been advanced that the pituitary change in the adrenogenital syndrome has just the same form both in Cushing's syndrome and in virilism, and that it is moreover independent of changes in other endocrine organs, with the

exception of the adrenal cortex. In these diseases, therefore, the pituitary change probably either expresses the direct cause, or is the direct result, of the adrenocortical hyperfunction characteristic of the adrenogenital syndrome.

It was stated in the survey of the literature that the menopausal syndromes ('Cushingoid habitus' and Syndroma Morgagni) show a clinical resemblance to the adrenogenital syndrome not only in the external main symptoms (obesity of 'buffalo type' and hirsutism), but also in raised concentration of the corticotropic factor in the blood (cf. in particular Broster *et al.* 1933, 1938; Henschen 1937, 1944; Bartelheimer *et al.* 1942). As a result of this investigation, it can now be added that an enlargement of the adrenal cortex is typical of the menopausal syndromes.

Naturally, it is not a foregone conclusion that an enlargement of the adrenal cortex implies hyperfunction there; on the other hand, there are cases where such hyperfunction is certain — *i. e.* cases of the adrenogenital syndrome — without gross changes in the cortex (cf. survey of the literature). Despite this, and despite the fact that adrenocortical adenomas, at any rate, occur quite as often without as with the adrenogenital symptoms, there is unquestionably a strongly positive correlation between pronounced pathological hyperplasia of the adrenal cortex (simple, adenomatous or cancerous) and symptoms of pathological hyperfunction of the adrenal cortex (= the adrenogenital syndrome). Or, in other words, there is no doubt that the typical, though not absolutely constant enlargement of the adrenal cortex in the adrenogenital syndrome is a morphological expression of its hyperfunction. — The same holds for the menopausal syndromes. Consequently, it is highly likely that the adrenocortical enlargement in the menopausal syndromes indicates hyperfunction. — The Ponceau-Fuchsin Reaction confirms this conclusion: positive reaction is typical of the menopausal syndromes, as also of adrenal virilism. That is to say, there are strong reasons for taking the menopausal syndromes to be mild forms of the adrenogenital disease. This bears out the conception vaguely envisaged by Achard and Thiers (1921), and more clearly ex-

pressed by Berblinger (1928), Broster and Vines (1933), and others.

As in the adrenogenital syndrome, the characteristic change of the anterior pituitary in 'Cushingoid habitus' and Syndroma Morgagni occurs apparently independent of each of the separate clinical main symptoms. On the other hand, it is positively correlated with the adrenocortical hyperplasia — the correlation is also suggested *in* the menopausal group. Consequently, in the menopausal syndromes, too, there is every probability that the typical pituitary change either expresses the direct cause or constitutes the direct result of adrenocortical hyperfunction.

The hypophysis and adrenal cortex in the collected material; conclusions concerning prostatic hypertrophy and the menstrual cycle. Men with prostatic hypertrophy admittedly show the characteristic pituitary change, but the criteria for hyperfunction of the adrenal cortex are far less certain than in the menopausal syndromes. It is true that there is a certain probability, even though faint (about 96: 100), that these men, too, are characterised by enlargement of the adrenal cortex. On the other hand, the prostatic hypertrophy group offers no clinical support for assuming this enlargement also to imply adrenocortical hyperfunction. Nor does the Ponceau-Fuchsin Reaction give clear information in men: for those with prostatic hypertrophy it shows no sure deviation from the normal material, but it does not show any sure deviation from the menopausal syndromes, either.

On the other hand, it is obvious that the strong positive correlation between hyperplasia and hyperfunction of the adrenal cortex found in the group adrenogenital syndrome + menopausal syndromes (compared with the corresponding normal material) makes it likely that hyperplasia of the adrenal cortex can, quite generally, indicate adrenocortical hyperfunction. It is therefore of particular interest to investigate the correlation of the typical pituitary picture (*i. e.* the frequency of hyaline basophiles + hypertrophic amphophiles) with the adrenocortical enlargement in the *whole* material of menopausal syndromes,

prostatic hypertrophy, and normal men and women. After all, even the normal cases showed a certain, generally quite low frequency of the special pituitary cells in point, and a suggested positive correlation between their frequency and the weight of the adrenal was observed *within* the normal group. For the *whole* of the material in point, the coefficient (according to Bravais-Pearson) for the correlation between the frequency of the special pituitary cells and the weight of the adrenal (49 cases) was $+ 0.36 \pm 0.12$; the corresponding coefficient for the correlation between the frequency of the special cells and the adrenocortical width (75 cases) was $+ 0.30 \pm 0.10$. The numerical values for the coefficients are admittedly rather small; nevertheless *each* is significantly positive, although they were established on partly different material, and although this material did not contain cases of the adrenogenital syndrome; needless to say, the latter cases would considerably raise the coefficients. To this can be added that the results from the investigated cases of diabetes mellitus, hyperparathyroidism and eunuchoidism do not argue against the correlation found.

Thus, the collected material shows with certainty a positive correlation between the typical pituitary change, characterised by hyaline basophiles and hypertrophic amphophiles, and enlargement of the adrenal cortex. No third factor could be shown to explain the correlation. The absence of such a third factor, inducing both the pituitary and the adrenocortical change, can admittedly not be proved in this way, but must be considered likely. Thus — in the collected material — it should be possible to assume the pituitary change to be either the expression of a corticotropic hyperfunction of the anterior pituitary, or the result of an adrenocortical hyperfunction.

It then becomes clear that, in all probability, a hyperfunction of the adrenal cortex also characterises men with prostatic hypertrophy, who, after all, have been shown with certainty to exhibit an average increase of the hyaline basophiles + hypertrophic amphophiles in the anterior pituitary.

Thus, the above-mentioned theory (pp. 40—41) that prostatic hypertrophy might be due to an adrenocortical hyperfunction

has received a certain morphological foundation. As was shown above, this conception finds particular support in Törnblom's observations of deficient growth of the seminal vesicles in prostatic cases compared with Davidson's finding (1937) that corticotropic pituitary extract in hypophysectomized rats has a far greater growth-promoting action on the prostate than on the seminal vesicles; the theory is also backed up by the Deming case (Deming *et al.* 1935) of prostatic hypertrophy in totally atrophic testes, as also by Spiegel's (1940) castration experiments with guineapigs. — On the other hand, an adrenocortical hyperfunction as the cause of prostatic hypertrophy does not agree with Törnblom's finding of normal concentration of comb-growth-promoting substance in the blood of prostatic cases (cf. pp. 40—41) when added to observations by Hooker and Collins (1940): the latter authors reported a stronger growth-promoting effect from desoxycorticosterone acetate on cock's-comb than on the prostate and seminal vesicles of rats and mice.

Nothing new has appeared concerning the possible part played by the testis in causing prostatic hypertrophy. The present author was unable to demonstrate any perceptible atrophy of the testicular germinative tissue in prostatic cases as compared with normal old men, this result thus arguing against an atrophy of the germinative tissue as prime cause of prostatic hypertrophy. On the other hand, the present author has been as little able as Teem (1935) to find any hyperplasia of the interstitial cells of the testis in prostatic cases, this suggesting that a hyperfunction of these cells plays no part in the genesis of the disease. It must, however, be admitted that the morphological investigations of the testis have a fairly limited value, not being quantitative.

The conclusion that increased frequency of hyaline basophiles and hypertrophic amphophiles in the anterior pituitary have in all probability a direct genetic correlation with hyperfunction of the adrenal cortex (p. 154) is plainly also true for those cases of the normal material who showed a raised frequency of the pituitary hyaline basophiles + hypertrophic amphophiles, *i. e.* the women towards the end of the menstrual cycle.

In other words, the end of the normal cycle is in all probability attended by raised adrenocortical function, primary or secondary in relation to the typical pituitary change.

The pituitary change as criterion for dysfunction or simple hyperfunction. The occurrence of the hyaline basophiles and hypertrophic amphophiles — as also weakly positive Ponceau-Fuchsin Reaction — both in the menopausal syndromes and in endocrinely normal subjects further allow of certain conclusions as to what significance the changes have as expressions of simple hyperfunction or dysfunction. Assuming that dysfunction implies a function of a quality only appearing in pathological states, its existence can be morphologically proved only by a morphological correlate, which similarly appears solely in pathological states. Gellerstedt's assumption (1939), previously shared by the present author (1942), that the hyaline basophiles expressed a dysfunction ('toxic' hyperfunction) typical only of the undoubtedly pathological 'pituitary basophilism' (Cushing's disease), but not of its constitutional counterpart ('Cushingoid habitus' and Syndroma Morgagni), cannot be upheld with morphological arguments. The same holds for the Ponceau-Fuchsin Reaction in the adrenal cortex (cf. above). Another thing is that Butler and Marrian (1937, 1938) have shown by hormone assays that a dysfunction of the adrenal cortex sometimes occurs in the adrenogenital syndrome; the morphological foundation of the dysfunction is not clarified, on the other hand.

The typical pituitary change: cause or effect of adrenocortical hyperfunction. The present author can only make a small contribution to the final question as to whether the pituitary or the adrenocortical disturbance is the primary functional derangement in the adrenogenital syndrome and in 'Cushingoid habitus' and Syndroma Morgagni; this contribution is the occurrence of numerous hyaline basophiles and hypertrophic amphophiles in the hypophysis of a case of Addison's disease. This finding definitely argues that this pituitary change cannot be secondary to a hyperfunction of the adrenal cortex.

However, it has been pointed out above that most of the previous observations point emphatically in the same direction, particularly the demonstration of an increased quantity of corticotropic factor in the blood of cases of the adrenogenital and the menopausal syndromes (Jores 1936; Berblinger 1940, 1943; Bartelheimer *et al.* 1942; and others), as also the possibility of experimentally inducing adrenal hyperplasia and virilism with corticotropic pituitary extracts (Hodler 1936, 1937; and others) and the possibility of inducing adrenocortical cancer by castration (Woolley *et al.* 1943; cf. p. 25). That adrenocortical adenomas and possibly also cancer may be complementary effects of the same superior incitement inducing adrenocortical hyperfunction in the menopausal syndromes, also, is suggested by the distribution of the fuchsinophile granules in two such cases of this material: in one case the Ponceau-Fuchsin Reaction was positive both in a cortical adenoma on one side and in the adrenal cortex on the other side, in the second the reaction was positive in the adrenal cortex on both sides, but not in the multiple small adenomas or in the incipient cancer focus which were present at the same time (cf. p. 129). On the other hand, it must be admitted that, in the adrenogenital cases where both an adrenal cancer and the remaining adrenal cortex were investigated for the Ponceau-Fuchsin Reaction, the reaction was positive only in the tumour.

Thus, it remains undecided which function in the adrenogenital disease (including menopausal syndromes) is the primary one, that of the pituitary or that of the adrenals; however, most arguments argue that the former is primary, that is to say, is the expression of a raised corticotropic function in the anterior pituitary.

It is finally worthy of mention that the discussion which has been conducted naturally does not exclude a *combination*, that is to say a reciprocally stimulating influence from the anterior pituitary and the adrenal cortex in the diseases discussed. This conception can be said to correspond to the well-known general tendency of pathological phenomena to describe a vicious circle. However, it derives no direct support from this work, and will therefore not be enlarged upon.

A SECONDARY FINDING still remains to be commented upon, namely the presence of hyaline basophiles among the cells 'invading' the posterior lobe. This phenomenon was noted in two cases of Cushing's disease (Tmb. Lund 1628/43 and O. Lund 450/43; observed even by C. G. Ahlström), in two cases with Syndroma Morgagni, in one man with prostatic hypertrophy, and in an endocrinely normal 58-year-old man (cf. Chapter V). The observation agrees with similar ones by Crooke (1935) and others, who saw a few hyaline basophiles in the posterior lobe in some cases of Cushing's disease. Thus, the phenomenon is rare and may occur in normal cases; it stands to reason, therefore, that it cannot have any very great independent importance for the genesis of the diseases under discussion. On the other hand, this occurrence of hyaline basophiles in the posterior lobe argues against the 'invading' basophiles being of another type than those in the anterior lobe, that is to say, argues against the special intermediate lobe basophiles in man, which have been upheld by some authors (cf. Floderus 1944).

SUMMARY

As is known, Cushing's syndrome and virilism are, broadly speaking, characterised by hyperfunction of the adrenal cortex — that is to say, they constitute clinical forms of the adrenogenital disease. Certain syndromes primarily found in women in the menopause have been regarded as mild forms of Cushing's syndrome on account of their clinical resemblance to this latter disorder. This has been assumed the case with Syndroma Morgagni, characterised by obesity, hirsutism and frontal enostoses, as also with the similar condition without enostoses, called 'Cushingoid habitus'. According to a theory of the present author, drawn up on the guidance of the earlier literature, it is possible that prostatic hypertrophy is also characterised by an adrenocortical hyperfunction. Hitherto, a regular pituitary change has been established only in one of the abovementioned disorders, namely Cushing's syndrome; thus, it is known that, in this syndrome, the anterior pituitary lobe is characterised by an abundance of hyaline basophiles (Crooke's cells), and is in addition often rich in hypertrophic amphophiles (large cells with amphophile, foamy or finely granulated protoplasm, and large, often polymorphous nuclei, usually poor in chromatin).

The present author has investigated the endocrine organs — particularly the hypophysis and adrenals — of 261 autopsy cases; of these, 16 had suffered from the adrenogenital syndrome, 45 from the menopausal syndromes, 28 from prostatic hypertrophy, 12 from certain other endocrine disturbances, and 160 were endocrinely normal. A particular method for counting the cells of the anterior pituitary was used, worked out for the purpose; the cell count was necessary to establish the relatively small germinal changes in this organ in Syn-

droma Morgagni, 'Cushingoid habitus' and prostatic hypertrophy.

The main points emerging from the investigation are:

1. The anterior pituitary lobe shows on the whole the same histological change in Cushing's disease, adrenal virilism, Syndroma Morgagni, 'Cushingoid habitus' and prostatic hypertrophy, namely, an increase of the number of hyaline basophiles and hypertrophic amphophiles, together with a less constant relative increase of the number of sparsely granulated basophiles. The only difference between the groups in point is that the pituitary change is quantitatively far stronger in Cushing's disease and adrenal virilism than in Syndroma Morgagni, 'Cushingoid habitus' and prostatic hypertrophy.

2. The observed pituitary change points purely morphologically to a hyperfunction of definite kind in the basophile cells, it being demonstrable that the hypertrophic amphophiles are in all probability developed from the basophiles, in part at any rate with hyaline basophiles as intermediate phase. As the structure of the above-mentioned cells indicate a hyperfunction, and seeing that the basophile granules are bearers of the corticotropic factor — two facts emerging from earlier investigations — it seems likely that the increased number of hyaline basophiles and hypertrophic amphophiles are the expression of a corticotropic hyperfunction of the anterior pituitary.

3. The fact that the whole material of adults showed a significantly positive correlation between the frequency of hyaline basophiles + hypertrophic amphophiles in the anterior pituitary and the size of the adrenal cortex (and no regular change in any other endocrine organ could be established to explain this correlation) also makes it seem likely that the pituitary change in point expresses corticotropic hyperfunction in the anterior lobe, for earlier literature on clinical and experimental aspects of the adrenogenital syndrome has already given strong reasons for supposing that the pituitary change is primary to the adrenal change. This also fits in well with the present author's observations in two cases of eunuchoidism and one case of Addison's disease.

4. The anterior pituitary's frequency of hyaline basophiles + hypertrophic amphophiles rises towards the end of the menstrual cycle, implying a probable increase of the corticotropic function of the hypophysis.

5. Two cases of hyperparathyroidism showed a special change in the anterior pituitary lobe, characterised by copious large chromophobes, probably degranulated basophiles.

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Errors.

P. 80, the last line, instead of $T = \frac{m}{28} \cdot t$, read $T = \frac{28}{m} \cdot t$.

P. 138, in table 41, one normal man has been wrongly referred to the third column instead of the fourth one. Thus in the table

instead of:	8 cases, 16 adrenals 5.71	6 cases, 12 adrenals 4.14	
	+ 0.07	+ 1.75	
read:	7 cases, 14 adrenals 5.56	7 cases, 14 adrenals 4.52	
	+ 0.22	+ 1.37	

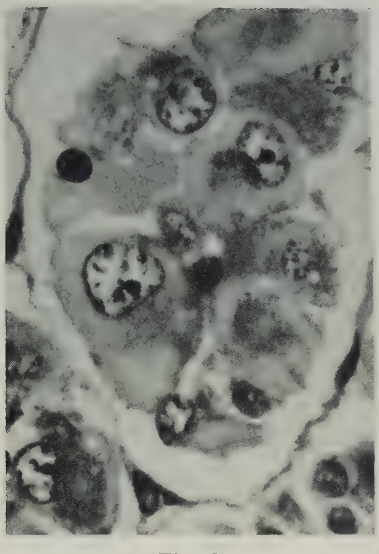


Fig. 2.

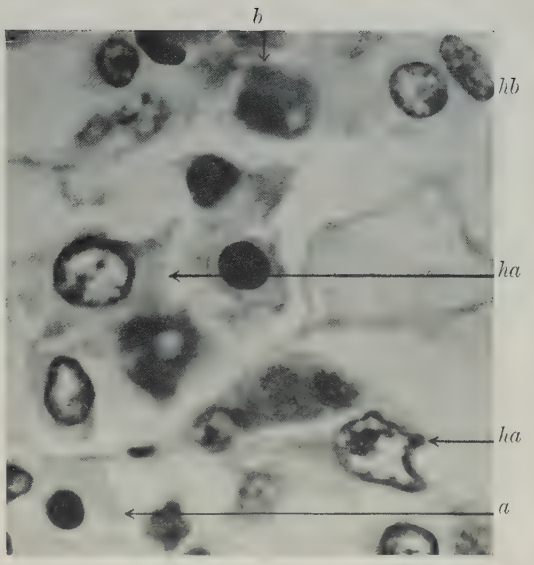


Fig. 3.

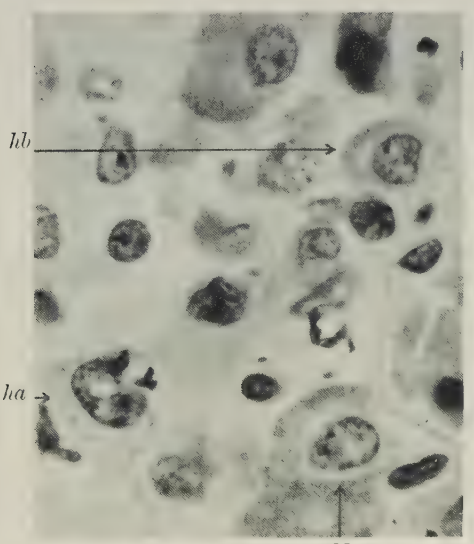


Fig. 4.

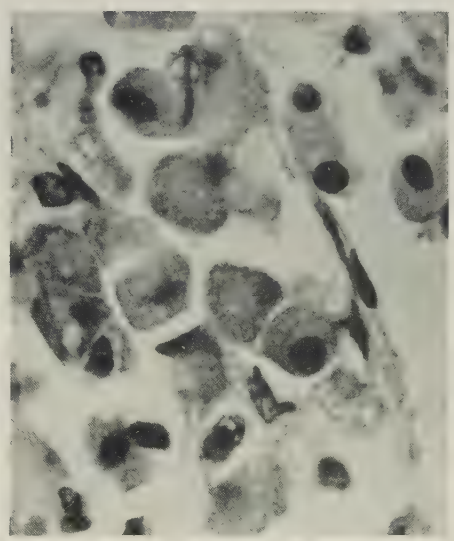


Fig. 5.

Fig. 2. Anterior pituitary from case 9, precocious puberty and Cushing symptoms in a 7-year-old boy. Numerous typical hyaline basophiles. — Htx-Magdala red. — × 1000.

Fig. 3. Ant. pit. from case 13, virilism in a 37-year-old woman. *ha* = hypertrophic amphophiles, *hb* = hyaline basophile, *a* = acidophile, *b* = basophile. — Htx-Magdala red. — × 1000.

Fig. 4. Ant. pit. from case 14, virilism in a 48-year-old woman. Symbols as in fig. 3. — Htx-Magdala red. — × 1000.

Fig. 5. Ant. pit. of an endocrinely normal, 17-year-old woman. (O. 26/43). Normal basophiles. — Htx-Magdala red. — × 1000.

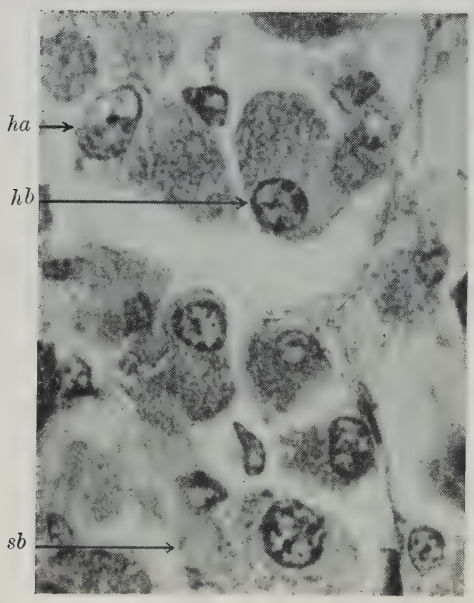


Fig. 6.

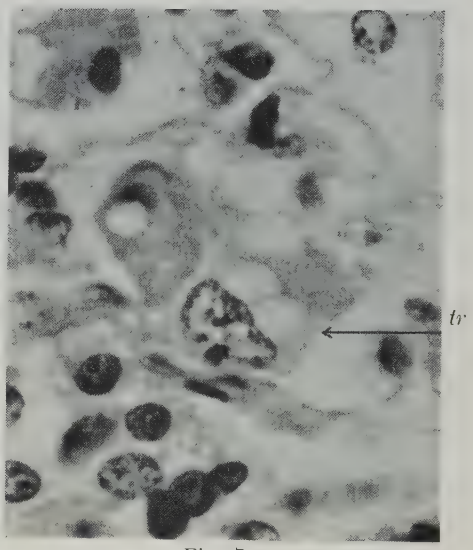


Fig. 7.

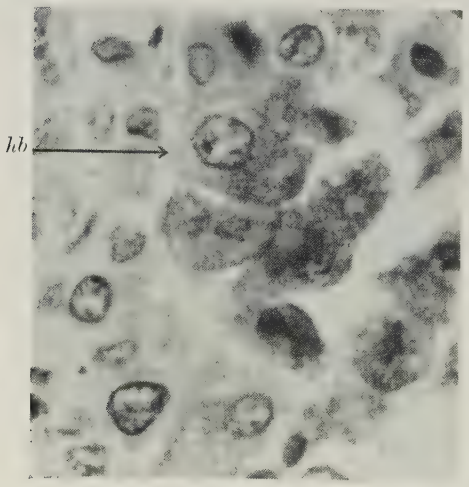


Fig. 8.

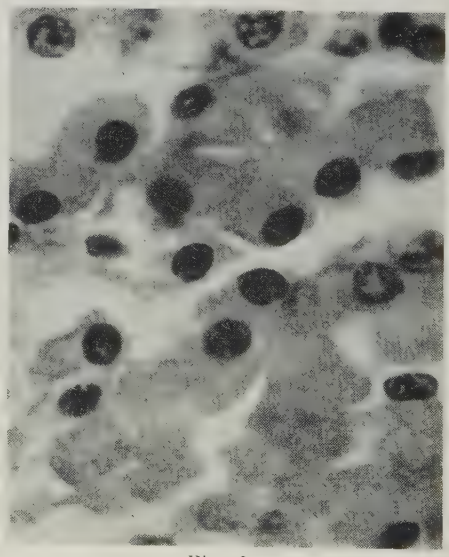


Fig. 9.

Fig. 6. Ant. pit. of a 69-year-old woman with Syndroma Morgagni (O. 399/43). Sparsely granulated basophile with large nucleus (*sb*), hyaline basophile (*hb*) and hypertrophic amphophile (*ha*). — Htx-Magdala red. — × 1000.

Fig. 7. Ant. pit. of an 85-year-old woman with Syndroma Morgagni (O. 422/42). Transitional cell between sparsely granulated basophile and hypertrophic amphophile (*tr*). — Htx-Magdala red. — × 1000.

Fig. 8. Ant. pit. of a 78-year-old man with prostatic hypertrophy (O. 130/44). Typical hyaline basophile (*hb*). — Htx-Magdala red. — × 1000.

Fig. 9. Ant. pit. of an endocrinely normal, 67-year-old woman (O. 54/44). Normal basophiles. — Htx-Magdala red. — × 1000.

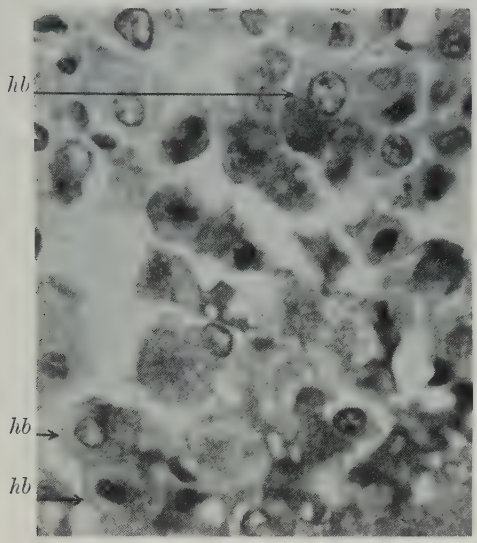


Fig. 10.

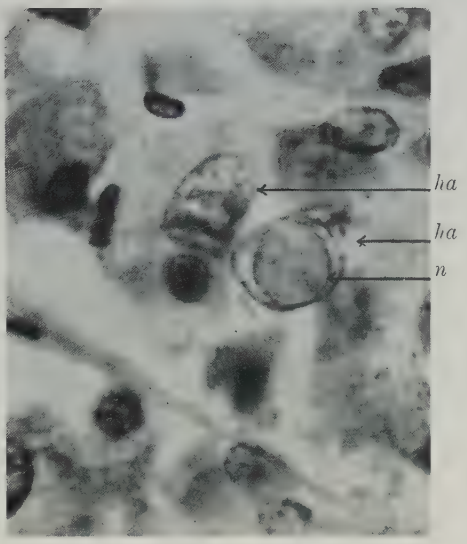


Fig. 11.

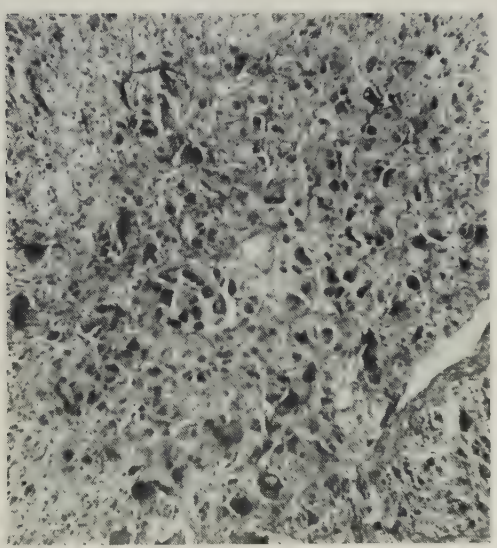


Fig. 12.

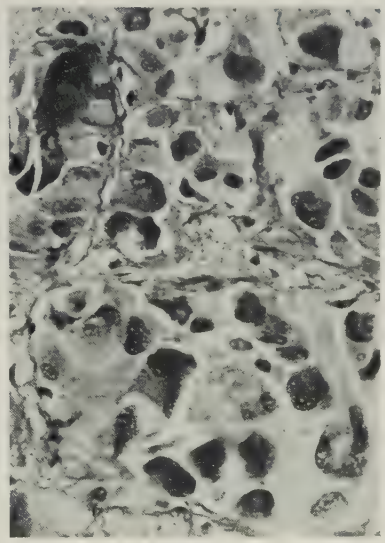


Fig. 13.

Fig. 10. Ant. pit. of a 78-year-old man with prostatic hypertrophy (O. 130/44). Hyaline basophiles (*hb*). — Htx-Magdala red. — × 700.

Fig. 11. Ant. pit. of a 56-year-old man with prostatic hypertrophy (O. 20/44). Typical hypertrophic amphophiles (*ha*), one of them with an enormous acidophile nucleolus (*n*). — Htx-Magdala red. — × 1000.

Fig. 12. Incipient cancer (?) of the adrenal cortex in a 66-year-old woman with Syndroma Morgagni (O. 54/43). — Ponceau-Fuchsin. — × 80.

Fig. 13. Central portion of fig. 16. — × 300. — Cf. the text, p. 127.

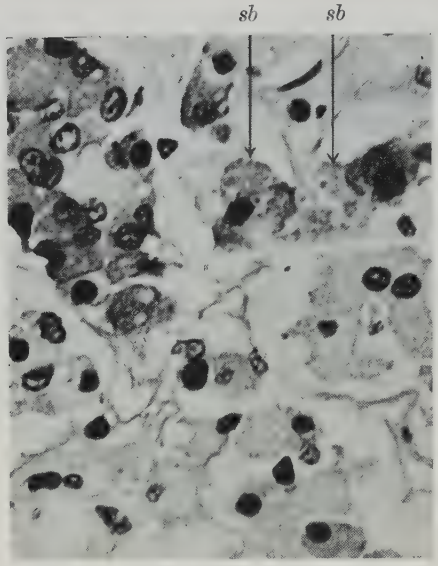
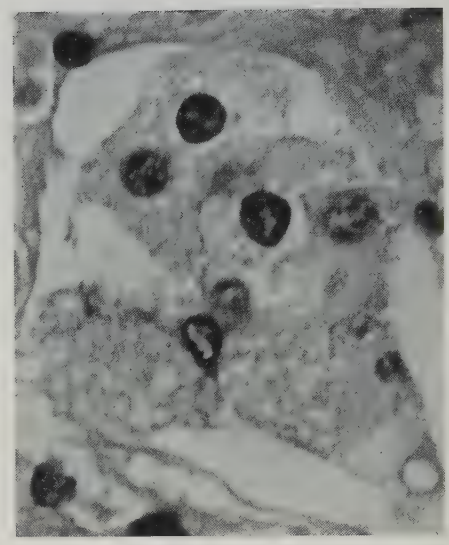


Fig. 14.



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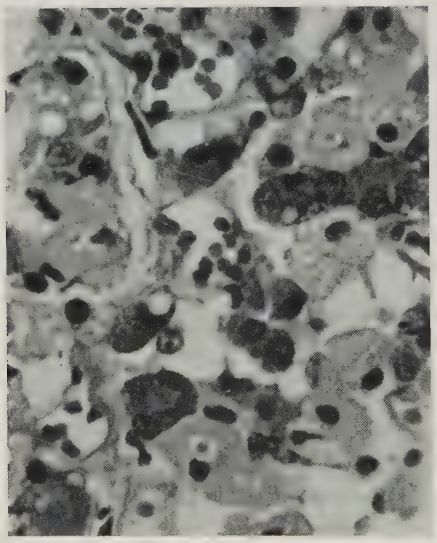

Fig. 16.

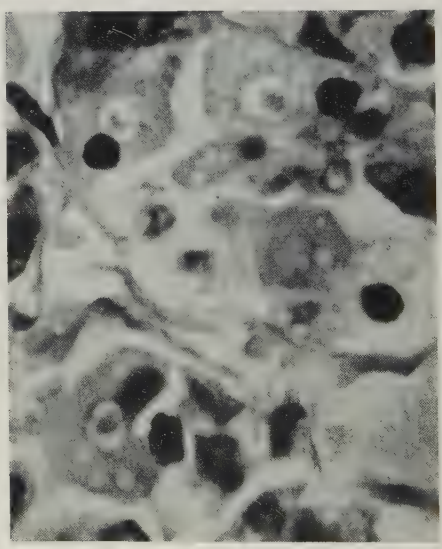

Fig. 17.

Fig. 14. Ant. pit. of a 56-year-old woman with hyperparathyroidism (O. 164/43). Chromophobes with large nuclei and very large cell bodies dominate. At *sb*, sparsely granulated basophiles. — Htx-Magdala red. — × 500.

Fig. 15. Ant. pit. in hyperparathyroidism (O. 164/43). Chromophobes with large nuclei and very large cell bodies; protoplasm foamy or loaded with minute chromophobe granules. — Htx-Magdala red. — × 1000. — Cf. fig. 14.

Fig. 16. Ant. pit. of a 57-year-old man with eunuchoidism (O. 220/42). Numerous pale basophiles with small nuclei, large cell bodies and hypertrophic Golgi zones (?); their protoplasm vacuolized, resembling colloid or clumped basophile granules. — Htx-Magdala red. — × 500.

Fig. 17. Ant. pit. in eunuchoidism (O. 220/42). — Htx-Magdala red. — × 1000. — Cf. fig. 16.

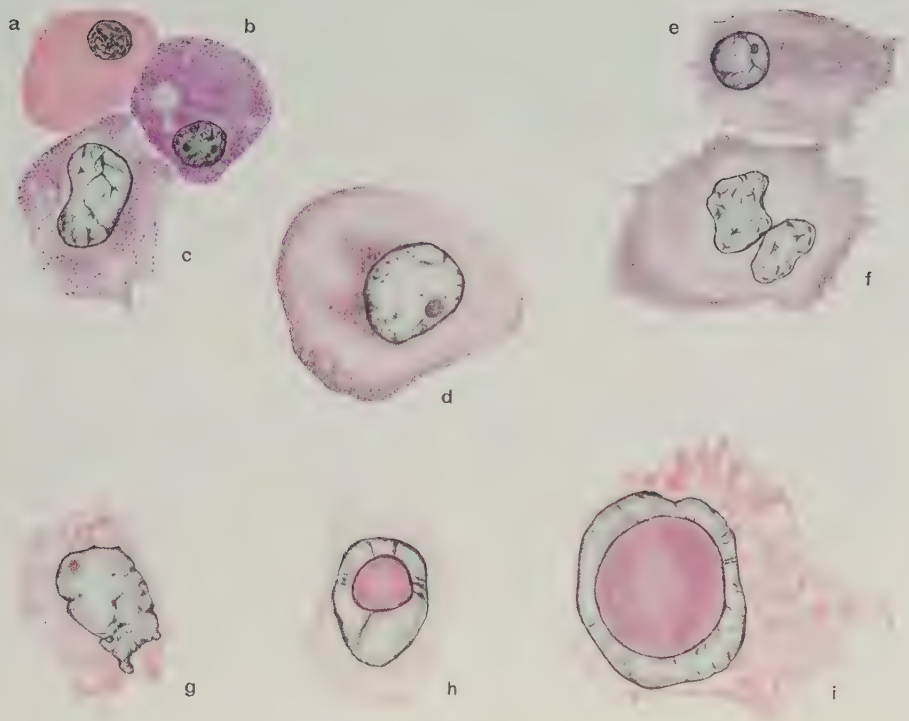

Fig. 18.

Fig. 18. Cell types of the anterior pituitary. a = normal acidophile; b = normal basophile; c = sparsely granulated basophile; d = typical hyaline basophile; e and f = atypical hyaline basophiles (cell contours not clear cut, in e small nucleus and partly foamy protoplasm); g, h, and i = hypertrophic amphophiles. — Htx-Magdala red. — About × 1500.

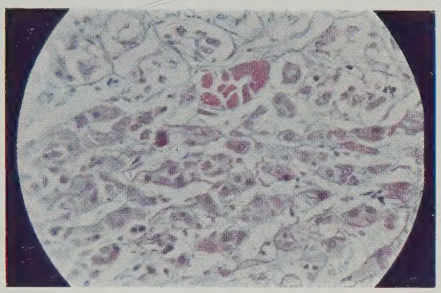

Fig. 19.

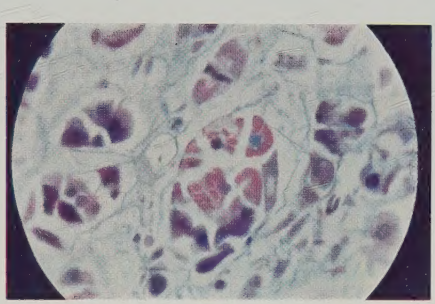

Fig. 20.

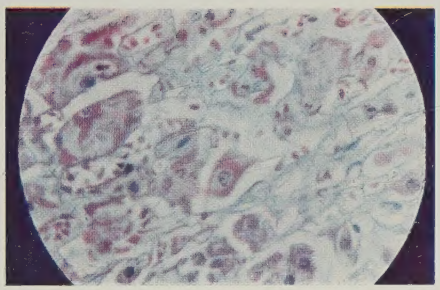

Fig. 21.

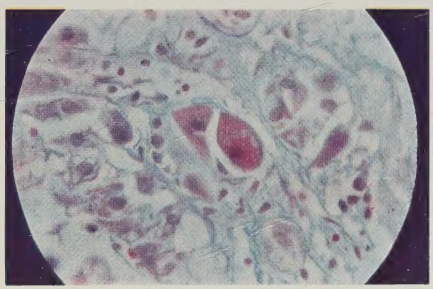

Fig. 22.

Fig. 19. Ponceau-Fuchsin Reaction positive in the adrenal cortex of an endocrinely normal, 38-year-old woman (O. 160/44). — × 135.

Fig. 20. Central portion of fig. 19. — × 300.

Fig. 21. Ponceau-Fuchsin Reaction positive in the adrenal cortex of a 78-year-old woman with Syndroma Morgagni (O. 192/44) — × 300.

Fig. 22. Ponceau-Fuchsin Reaction positive in the adrenal cortex of an 82-year-old man with prostatic hypertrophy (O. 30/44). — × 300.

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